Registered at the G.P.O., Sydney, for Transmission by Post as a Newspaper. Published Weekly. Price 1s.

THE MEDICAL JOURNAL OF AUSTRALIA

VOL. I.—16TH YEAR. SYDNEY, SATURDAY, MARCH 23, 1929. No. 12.

THE MEDICAL JOURNAL OF AUSTRALIA

VOL. I.—16TH YEAR. SYDNEY, SATURDAY, MARCH 23, 1929. No. 12.

Authors of articles submitted for publication are requested to read the following instructions and to comply with them.

All articles must be typed with double or treble spacing. Carbon copies should not be sent. Abbreviations should be avoided, especially those of a technical character at times employed in ward notes. Words and sentences should not be underlined or typed in capitals. The selection of the correct type is undertaken by the Editors. When illustrations are required, good photographic prints on glossy gaslight papers should be submitted. Each print should be enclosed in a sheet of paper. On this sheet of paper the number of the figure and the legend to appear below the print should be typed or legibly written. On no account should any mark be made on the back of the photographic print. If no good print is available, negatives may be submitted. Line drawings, graphs, charts and the like should be drawn on thick, white paper in India ink by a person accustomed to draw for reproduction. The drawings should be large and boldly executed and all figures, lettering and symbols should be of sufficient strength and size to remain clear after reduction. Skiagrams can be reproduced satisfactorily only if good prints or negatives are available. The reproduction of all illustrations but especially of skiagrams entails the sacrifice of time and energy and is expensive. Authors are expected to take a corresponding amount of trouble on the preparation of their illustrations, whether skiagrams, photographs, wash drawings or line drawings. The references to articles and books quoted must be accurate and should be compiled according to the following scheme. The order should correspond to the order of appearance in the article. The initials and surnames of the authors, the full title of the article or book, the full (unabbreviated) title of the journal in which the article appears, the date of the issue (day, month and year) and the number of the first page should be given in this sequence.

Table of Contents

Symposium on Snake Bite.

A PRELIMINARY NOTE ON THE VENOM OF PSEUDECHIS GUTTATUS.[1]

By C. H. KELLAWAY, M.C., M.D., M.S., M.R.C.P. (London).
From the Walter and Eliza Hall Institute, Melbourne.

A single specimen of *Pseudechis guttatus*, measuring ninety-eight centimetres in length, was obtained from Dulacca, Queensland, by Mr. T. E. Eades during a field excursion for the purpose of collecting death adders for investigation at this institute. As no previous observations have been made either on the pharmacological nature of the venom or on the quantity of poison ejected during biting, it was thought worth while to record our observations along these lines. I am indebted to Dr. N. Hamilton Fairley for the following notes on the snake itself and on its biting apparatus and venom yields.

De Vis[(1)] first described the external characteristics of *Pseudechis guttatus*, pointing out how it could be differentiated from *Pseudechis papuanus* by its colouring, the altered proportions of certain of its cephalic shields, the reduced number of its ventral plates and the presence of paired subcaudal scales. In all essential features our specimen corresponded with the accurate and detailed description of De Vis.

External Characteristics.

In colour the upper surface was a coppery black speckled with yellowish grey spots extending from the neck downwards for three-quarters of its length, while the lower surface was of a leaden grey hue, the ventrals being tipped with grey or mottled with brown. The head was distinct from the neck, though the separation was not pronounced; the eyes were rounded, the pupils circular and the iris dark brown in colour.

The upper part of the head had the large, regular nine shields as well as the six supralabials so characteristic of the Australian poisonous snakes.

The rostral shield was broader than it was deep, the internasals were about half the length of the prefrontals and the frontal was much larger again. The latter shield was half as long as it was broad.

There were two postocular scales and the postnasal was in touch with the single preocular. The lower large anterior temporal scale was wedged between the fifth and sixth supralabial scales, while the third and fourth supralabials entered the orbit. The chin shields were equal, the anterior being in contact with the four lower labials. The scales round the body numbered nineteen to twenty and the rounded ventral plates totalled 191.

The subcaudal scales numbered 58, the terminal eleven being doubled and the remainder single. In De Vis's specimen the ventrals equalled 181 and the subcaudals fifty, of which eleven were paired. The anal scale was divided.

Biting Apparatus and Venom Yields.

In captivity the snake is both aggressive and savage, hissing loudly and flattening out like a tiger snake when annoyed. It strikes with the mouth shut and presents no peculiarities meriting a special description.

Certain osteological features may be briefly described. The maxillary bones extend as far forward as the palatines and in our specimen there were two recurved poison fangs lying side by side on the left maxilla, one being a reserve fang which was coming into position (see Figure XVI, page 316). The usual single fang was present on the right maxilla. Three small postmaxillary teeth projected from the left and two from the right maxilla just anterior to the junction with the ectopterygoid. The small recurved pterygo-palatine teeth numbered twenty-one on the right and nineteen on the left side.

The fangs measured 3·5 millimetres (one-seventh of an inch), were anteriorly grooved and curved backward. They were capable of slight forward rotation when the pterygoid was carried forward by contraction of the spheno-pterygoid muscle.

Impressions of the bite taken in Kerr's impression compound showed three fang marks, the extra one being due to the advanced position of the left reserve fang already referred to. The distance between the fangs was 1·2 centimetres and both the postmaxillary and the pterygo-palatine teeth were clearly outlined in the dental matrix.

The snake bit with avidity and when milked at monthly intervals yielded 25·1, 50·2 and 16·0 milligrammes of dried venom which formed the typically yellow pseudo-crystals seen in the case of other venomous snakes.

Our observations showed that with the exception of the death adder the biting mechanism and venom yields of *Pseudechis guttatus* compared favourably with other poisonous Australian colubrides of similar dimensions.

THE VENOM.

As only a small quantity of venom was available, it seemed expedient to determine the certainly lethal dose for several of the smaller laboratory animals, though the amount of material was insufficient for its complete characterization in these.

Effects in Rabbits.

In rabbits only a few observations were made. Injected intravenously into the ear vein, in concentration of 0·2 milligramme per cubic centimetre and in doses ranging from 0·1 to 0·9 milligramme per kilogram it produced the results recorded in Table I.

TABLE I.
Results of Intravenous Injection in Rabbits.

Weight in Kilograms.	Dose in Milligramme per Kilogram.	Result.
1·62	0·9	Death in 30 minutes.
2·7	0·8	Death in 1 hour 20 minutes.
1·65	0·6	Death in 4 hours 50 minutes.
1·83	0·6	Death in 6 hours.
1·65	0·5	Death in 2 hours 55 minutes.
1·55	0·5	Weakness of hind limbs for an hour or two, ataxic and off food, recovered in 6 hours.
2·45	0·4	Death in 3 hours.
1·38	0·2	Slight transient weakness of the hind limbs; after half an hour, quick recovery.
1·87	0·1	No symptoms.

The symptoms following the fatal injections were very uniform. There was a quiet gradual loss of tone of the musculature of the body, the head falling over on one side and the body ultimately falling on one side. At a late stage there was respiratory distress and sometimes terminal convulsions.

Post Mortem Findings.

There were usually hæmorrhages in the lungs and occasionally in the adrenals. The small intestine, the liver, kidneys and spleen and (in the female) the uterus were intensely congested and in some cases severe hæmoglobinuria was present. The clotting time was delayed and varied between twenty minutes and nine hours. Somewhat surprisingly no obvious clotting was found in the vessels or heart in the animals examined immediately after death.

In a few rabbits the venom was administered subcutaneously in the abdominal wall in a concentra-

[1] This research was carried out under a grant from the Commonwealth Government Department of Health.

tion of 1·0 milligramme per cubic centimetre with the following results (see Table II).

TABLE II.

Results of Subcutaneous Injection in Rabbits.

Weight in Kilograms.	Dose in Milligramme per Kilogram.	Result.
1·9	2·0	Death between 10 and 21 hours.
2·36	1·0	Death between 30 and 42 hours.
1·65	0·6	Survived.

The symptoms and *post mortem* findings were similar to those observed following intravenous injection.

There appears to be no very marked difference between the certainly lethal dosage by these two methods of administration. By the subcutaneous route the three observations made suggest that it may lie between 0·6 and 1·0 milligramme per kilogram, while 0·6 is fatal, though much more rapidly by the intravenous method of administration. The intense congestion in the portal tract in these latter animals suggests that some degree of thrombosis had occurred in the portal circulation, though this was not observed at autopsy.

Effects in Guinea-Pigs.

In guinea-pigs the effect of intravenous injection was observed in a few animals only (see Table III), the venom being used in a concentration of 0·1 milligramme per cubic centimetre and the injections being made into the jugular vein under local cocaine anæsthesia.

TABLE III.

Results of Intravenous Injection in Guinea-pigs.

Weight in Grammes.	Sex.	Dose in Milligramme per 100 Grammes.	Result.
232	Male	0·06	Death in 2 hours 50 minutes.
237	Male	0·04	Death in less than 11 hours.
268	Female	0·04	Survived.
269	Female	0·04	Survived.
265	Female	0·04	Death in 7 hours 40 minutes.
268	Female	0·04	Death in 4 hours.
258	Female	0·03	No definite symptoms; survived.
273	Female	0·03	No symptoms; survived.
203	Male	0·02	Survived.

The certainly lethal dose is probably about 0·06 milligramme per hundred grammes of animal.

The symptoms exhibited by these animals were similar to those exhibited by guinea-pigs which received the venom subcutaneously; they will shortly be described.

Post Mortem Findings.

In the rapid deaths there were hæmorrhages in the lungs. The kidneys, the mucous lining of the stomach and the adrenals were intensely congested, as also was the small intestine which was frequently filled with bile stained mucus. In some animals clotting had taken place in the heart and vessels.

The later deaths presented *post mortem* changes like those observed in animals injected subcutaneously and they resembled those following the injection of diphtheria toxin.

A larger number of observations in guinea-pigs weighing from 230 to 300 grammes was made after subcutaneous injection in the abdominal wall with venom in a concentration of 0·2 milligrammes per cubic centimetre.

Table IV summarizes these results.

TABLE IV.

Results of Subcutaneous Injection in Guinea-pigs.

Number of Animals.	Dose in Milligramme per 100 Grammes.	Result.
2	0·27	Died in 2 hours 45 minutes and in 3 hours 55 minutes.
2	0·23	Died in 2 hours 30 minutes and in 3 hours 20 minutes.
2	0·2	Died in 4 hours 43 minutes and in less than 23 hours.
2	0·17	Died in 5 hours 30 minutes and in less than 13 hours.
2	0·13	Died in 5 hours 30 minutes and in less than 13 hours.
2	0·1	Both died in less than 13 hours.
6	0·08	Died in 11 hours, 12 hours, 16 hours, 17 hours, 17 hours, and in less than 37 hours.
8	0·07	Two survived, the remainder died in 14 hours, 17 hours, 17½ hours, 18½ hours, 45 hours, and 62 hours.
8	0·06	Two survived, the remainder died in less than 13 hours, 15½ hours, 16 hours, 19½ hours 24 hours, and 29½ hours.
5	0·05	Two survived, the remainder died in 23 hours, 24½ hours, and 2 days.
5	0·04	Four survived, one died in 45 hours.
2	0·03	Both survived.

The certainly lethal dose is in the neighbourhood of 0·08 milligramme per hundred grammes of guinea-pig, a dose not greatly in excess of that which proves fatal when administered intravenously, though this last value has been determined only approximately. The numbers of observations are too small to define the "characteristic" for this venom by plotting the percentage mortality against the dose (Shackell,[2] Trevan[3]).

In most of the animals the symptoms were not striking during the first few hours. For an hour or more before death the coat was staring, there was obvious dyspnœa, some paresis of the hind limbs, dilatation of the pupils in some cases, occasional "starting movements" and finally collapse and death. It was not uncommon for animals injected with this venom to collapse suddenly and die rapidly in the course of half an hour without showing definite symptoms earlier.

Post Mortem Findings.

The changes observed were strikingly similar to those produced by the injection of diphtheria toxin. There was intense œdema, which was frequently hæmorrhagic, spreading from the site of injection in the abdominal wall from the sternum to the pubis and often nearly a centimetre in thickness. There was intense hæmorrhagic congestion of the adrenals. The pleural and peritoneal cavities were always wet; sometimes there was hydrothorax or the effusion of blood stained fluid. Hæmorrhages

in the lungs were constant, the small intestine was usually filled with bile stained mucus and sometimes there was intense hæmorrhagic congestion affecting the whole length of the small intestine. Hæmoglobinuria in animals dying after twenty-four hours was frequent. In pregnant animals hæmorrhage usually occurred into the uterus. The coagulation of the blood was delayed, one to two hours being required for the coagulation of samples of blood withdrawn from the heart immediately after death.

Effects in the Rat.

A few observations were made in rats weighing from 130 to 160 grammes, the venom being introduced into one of the tail veins in a concentration of 0·1 milligramme per cubic centimetre (see Table V).

TABLE V.

Results in Rats Injected Intravenously.

Number of Animals.	Dose in Milligramme per 100 Grammes.	Result.
1	0·08	Death in 20 minutes.
4	0·04	One survived, the remainder died in 54 minutes, in 2 hours 7 minutes, and in 2 hours 13 minutes.
4	0·03	One survived, two died in 26 minutes and one in 4 hours 32 minutes.
3	0·02	Two survived and one died in less than 15 hours.
3	0·01	All survived.

The certainly lethal dose by this route would appear to be somewhat in excess of 0·04 milligramme per hundred grammes. The symptoms observed were dyspnœa and staring coat, weakness of hind limbs and collapse, strong convulsions alternating with periods of quiet collapse. The pupils were contracted in some and in others dilated. In the case in which death occurred quickly and in one or two others the collapse and convulsions were obviously due to portal thrombosis.

Post Mortem Findings After Intravenous Injection.

Although in only one or two animals was intravascular thrombosis observed, in the majority of the animals congestion of the spleen and small intestine was seen. There were frequently hæmorrhages in the lungs. Following the largest dose the coagulation of the blood was very greatly delayed and in most cases the clotting time of blood taken from the heart immediately after death varied between fifteen and twenty-four minutes.

Subcutaneous injections in the flank were made with venom solutions containing 0·5 milligramme per cubic centimetre in rats varying in weight between 130 and 180 grammes.

The following results were obtained (see Table VI).

The certainly lethal dose is in the neighbourhood of 0·07 milligramme per hundred grammes.

The animals had a staring coat and slight dyspnœa and often hæmoglobinuria. Weakness of the hind limbs and ataxic gait were frequently present early; later the animals lay prone with profound collapse. In some death occurred very suddenly, the animals appearing moderately well and presenting only slight symptoms till immediately before death.

TABLE VI.

Results in Rats Injected Subcutaneously.

Number of Animals.	Dose in Milligramme per 100 Grammes.	Result.
1	0·66	Death in 2¾ hours.
1	0·51	Death in 3 hours 10 minutes.
1	0·42	Death in 6 hours.
1	0·29	Death in 3 hours 20 minutes.
3	0·14	Death in 6 hours 50 minutes, in less than 14 hours, and in 23 hours.
1	0·13	Death in 3 days.
3	0·12	All died in less than 14 hours.
2	0·11	Death in less than 14 hours and in 18 hours.
2	0·1	Death in less than 14 hours and in 3 days.
3	0·09	Death in 19¼ hours, between 26 and 41 hours, and in 3 days.
3	0·08	Death in less than 14 hours, in 23½ hours, and in 18 hours.
5	0·07	Two died in less than 14 hours, one in 20 hours, one in 22 hours, and one in five days.
10	0·06	Six survived, and the remainder died in 18 hours, 22 hours, 31 hours, and 4 days.
10	0·05	One died in 22 hours, two in 2 days, one in 2¼ days, two in 3 days, and four survived.

Post Mortem Findings After Subcutaneous Injection.

There was much hæmorrhagic œdema at the site of inoculation, gravitating towards the middle line of the abdominal wall. There was more hæmorrhage and less œdema than in guinea-pigs.

In the late deaths (after several days) the œdema was not present and the tissues were stained with altered blood. Hæmorrhages in the lungs were not constant and, though sometimes gross, were generally slight in extent. There was frequently hæmorrhagic enteritis and in other cases the small gut was filled with bile stained mucus.

In females the uterus was intensely congested and in pregnant animals small hæmorrhages were to be seen in the fœtus. Occasionally there were petechial hæmorrhages in the adrenals. Hydrothorax sometimes was found. There was no obvious change in the clotting time. In some of the animals dying late no naked-eye changes other than wasting were found at autopsy.

Effects in Mice.

In mice weighing between eighteen and twenty-two grammes the venom in a concentration of 0·2 milligramme per cubic centimetre was injected into one of the tail veins, with the results recorded in Table VII.

TABLE VII.

Results in Mice Injected Intravenously.

Number of Animals.	Dose in Milligramme per 20 Grammes.	Result.
4	0·05	Death in 17, 20, 27, and 29 minutes.
4	0·04	Death in 13, 30, 31, and 40 minutes.
4	0·03	Death in 32, 41, 45, and 45 minutes.
5	0·02	Death in 45, 68, 78, 80, and 136 minutes.
5	0·01	One survived, and the others died in 1 hour 34 minutes, 1 hour 44 minutes, 2 hours, and in 3 hours 33 minutes.
3	0·008	Two survived and one died 2 days later.

The certainly lethal dose for mice by the intravenous route is, therefore, in the neighbourhood of 0·02 milligramme per 20 grammes.

In the animals that died rapidly, the first symptoms noted were dyspnœa, paralysis of the hind limbs and collapse. Convulsions of asphyxial origin were present in many and often ushered in the collapse. In those which died more slowly, there were twitching and "starting movements" with occasional convulsions.

Post Mortem Findings After Intravenous Injection.

All these animals showed hæmorrhages of varying size in the lungs. Nearly all presented intense hæmorrhagic congestion of the small intestine and congestion of the spleen. Hæmoglobinuria was evident in most of those in which the bladder contained urine at autopsy. In a few the adrenals were congested. The blood in the heart was in all cases fluid and the clotting time (two observations) was not greatly delayed. No clots were observed in the larger portal vessels, but some degree of thrombosis was almost certainly present in the portal system.

The results of the subcutaneous injection into mice weighing eighteen to twenty-two grammes, of venom in a concentration of 0·2 milligramme per cubic centimetre are given below (see Table VIII).

TABLE VIII.

Results of Subcutaneous Injection in Mice.

Number of Animals.	Dose in Milligramme per 20 Grammes.	Result.
1	0·8	Death in 53 minutes.
1	0·4	Death in 1 hour 27 minutes.
1	0·2	Death in 2 hours 14 minutes.
1	0·1	Death in 7 hours 45 minutes.
4	0·09	Two died in less than 5½ hours and two in less than 13 hours.
4	0·08	Three died in less than 5½ hours and one in 13 hours.
4	0·07	Three died in less than 5½ hours and one in 20½ hours.
4	0·06	All died in less than 5½ hours.
5	0·05	One died in less than 5½ hours, three in less than 13 hours, and one on the third day.
8	0·04	Seven survived and one died on the fifth day.
8	0·03	Six survived and two died in less than 24 hours.

The certainly lethal dose was about 0·05 milligramme for a mouse of 20 grammes.

The symptoms exhibited by these animals were not very different from those presented after subcutaneous injection in rats. They had ruffled coats, dyspnœa of varying severity and paralysis of the hind limbs leading to collapse and death.

Post Mortem Findings After Subcutaneous Injection.

There was intense hæmorrhagic œdema spreading from the site of the injection (the left flank) to the abdominal wall. The lungs showed hæmorrhages of varying extent. The adrenals were sometimes and the kidneys almost invariably congested. Hæmoglobinuria was frequent. In females the uterus was congested. Bile stained mucus was present in the small intestine and in one or two cases there was actual hæmorrhage into the lumen.

Injections in Sheep.

Owing to the small amount of venom available, only two animals were injected. The first sheep which weighed 53·2 kilograms, received two milligrammes in 0·2 cubic centimetre of saline solution into the jugular vein, that is 0·038 milligramme per kilogram. No untoward symptoms developed. Into the subcutaneous tissues of the foreleg of the second animal 10·6 milligrammes were injected in physiological saline solution, equivalent to ten milligrammes to the cubic centimetre. As this sheep weighed 35·45 kilograms, it received the equivalent of 0·3 milligramme per kilogram. The animal looked ill and went off its feed temporarily, but the secretions and excreta remained normal and dyspnœa, paresis and salivation were never observed. Within two days the animal had completely recovered and the local swelling induced at the site of the injection had subsided.

In general the results of the injection of this venom into animals indicate that except in mice there is no very large difference between the amount which is certainly lethal, whether administered intravenously or subcutaneously, as Table IX shows.

TABLE IX.

Summary of Certainly Lethal Dose of Pseudechis guttatus.

Animal.	Certainly Lethal Dose.	
	Intravenous.	Subcutaneous.
Sheep ..	—	More than 0·3 milligramme per kilogram.
Rabbit ..	About 0·6 milligramme per kilogram.	Probably lies bewteen 0·6 and 1·0 milligramme per kilogram.
Guinea-pig	About 0·06 milligramme per 100 grammes.	0·08 milligramme per 100 grammes.
Rat	Between 0·04 and 0·08 milligramme per 100 grammes.	0·07 milligramme per 100 grammes.
Mouse ..	0·02 milligramme per 20 grammes.	0·05 milligramme per 20 grammes.

It should, however, be borne in mind that the values given here are only approximate, as the numbers of animals injected are in all cases too small for accurate estimation of the certainly lethal dose.

There is no doubt that a thrombase is present, though this venom is not so active in this respect as that of *Notechis scutatus* (tiger) or *Pseudechis porphyriacus* (black). Readily recognizable intravascular thrombosis was only once or twice observed after intravenous injections, though the symptoms and the *post mortem* finding of marked congestion in the portal tract indicated its presence.

Further evidence in this direction was afforded by the coagulation of citrated plasma. One such experiment was made with the results given below, sheep plasma obtained by diluting five cubic centimetres of blood with an equal volume of 2% sodium citrate in normal saline solution being used. The

tubes were 1·2 centimetres in diameter. The volume of plasma in each tube was 0·5 cubic centimetre and the venom solution was added with a dropping pipette. The experiment was carried out at 38° C..

TABLE X.
Clotting Time.

Amount of Venom Added in Milligramme.	Clotting Time.
0·05 0·1	Not clotted in 20 hours.
0·15	50 minutes.
0·2	45 minutes.
0·3	40 minutes.
0·4	30 minutes.
0·5	30 minutes.

The hæmolytic activity of the venom is indicated by the appearence of intense hæmorrhagic œdema at the site of injection and by the hæmoglobinuria, often extremely severe, in all the species examined.

It was tested directly by a hæmolysis experiment *in vitro* with the use of a 3% suspension in Ringer's solution (with a hydrogen ion concentration of 7·4) of sheep, ox and human corpuscles. No attempt was made to find the limits of hæmolysis of the venom, but its activity was compared with that of *Notechis scutatus*. Both venoms were dissolved in Ringer's solution (one milligramme per cubic centimetre). The total volume of the system in each case was 0·4 cubic centimetre, 0·2 cubic centimetre of venom solution, 0·1 cubic centimetre of complement (one part in ten of guinea-pig's serum equals four minimum hæmolytic doses), of human or sheep sera (inactivated) or of saline solution and 0·1 cubic centimetre of red blood corpuscles.

The readings were taken after three hours at 37° C. and one at room temperature and after twenty hours at room temperature.

TABLE XI.
Hæmolytic Action of Venom.

Common Ingredients: Venom and Red Blood Corpuscles.	Time in Hours.	Varying Ingredients.			
		Saline.	Complement.	Sheep Serum.	Human Serum.
Notechis scutatus.					
Sheep	4	−	−	−	−
	20	tr.	tr.	−	−
Ox..	4	−	−	−	−
	20	tr.	+	tr.	−
Human	4	−	−	−	−
	20	+++	+	+	+
Pseudechis guttatus.					
Sheep	4	++	tr.	−	−
	20	+++	+	−	−
Ox..	4	++	+	tr.	tr.
	20	+++	+++	++	++
Human	4	+++	++	++	tr.
	20	+++	+++	+++	++
Without venom.					
Sheep	4	−	−	−	+
	20	−	+	−	+
Ox..	4	−	−	−	−
	20	−	+	−	−
Human	4	−	−	−	−
	20	++	+	+	−

It is apparent that the hæmolytic power of *Pseudechis* is much greater than that of *Notechis* in an equal concentration and that without the addition of complement it readily hæmolyses the corpuscles of the three species investigated. The experiment also shows very well the protective power of serum in the case of sheep corpuscles.

The cytolytic activity of the venom, at all events as far as endothelium is concerned, is indicated by the hæmorrhagic œdema at the site of injection and by the almost invariable hæmorrhages in the lungs (usually extensive), adrenals and in other regions.

The venom resembles that of other Australian colubrides in possessing a powerful stimulant action on the isolated plain muscle of the guinea-pig. Once a reaction has been produced by a sufficient dose, a second dose is without effect. This phenomenon is at present under investigation and the results so far obtained suggest that it is not directly due to action on nerve endings nor on the plain muscle itself, but to the liberation of a stimulant substance possibly by cytolysis. In the case of *Pseudechis* venom the limits of the phenomenon have not been tested, but the reaction of the isolated uterus of the guinea-pig is maximal in a concentration of 1 in 100,000 of this venom.

The neurotoxic activity of the venom is evidenced by the symptoms presented in animals after subcutaneous injection, though many of the nervous manifestations are doubtless asphyxial in origin.

COMPARISON OF THE VENOM WITH THAT OF OTHER AUSTRALIAN COLUBRIDES.

In sheep the approximate certainly lethal dose on subcutaneous injection (Fairley) is 0·01 milligramme per kilogram for tiger snake venom, 0·025 milligramme for death adder, 0·1 milligramme for the copper-head and certainly not less than 0·8 milligramme for the black snake. With *Pseudechis guttatus* 0·3 milligramme entirely failed to produce paretic symptoms. Evidently for ovines the certainly lethal dose is more nearly related to that of the black snake than to the other Australian colubrides reviewed in the text.

The certainly lethal dose of venom of the Australian colubrides on subcutaneous injection into the rabbit are approximately as follows in milligrammes per kilogram: Tiger 0·05 (Martin and Tidswell), death adder 0·15 (Kellaway), brown 0·2 (Tidswell), black 0·6 (Martin and Tidswell), copper-head 0·7 (Kellaway), *Pseudechis guttatus* probably between 0·6 and 1·0.

For the guinea-pig the figures in milligrammes per hundred grammes are: Tiger about 0·002 (Kellaway), copper-head 0·006 (Kellaway), death adder 0·015 (Kellaway), *Pseudechis guttatus* 0·06, black 0·25 (Kellaway).

For the rat the fatal subcutaneous doses in milligrammes per hundred grammes are: Tiger about 0·04 (Kellaway), *Pseudechis guttatus* 0·07, copper-head 0·14 (Kellaway), black about 0·25 (Kellaway).

For the mouse the lethal doses in milligrammes per twenty grammes are: Tiger 0·005 (Kellaway), *Pseudechis guttatus* 0·05, copper-head 0·024 and death adder 0·014.

Some of the figures given here are based on too small a number of observations to possess final accuracy. They do, however, illustrate the value of making observations in more than one species for the purpose of comparing the toxicity of venoms. While it is not possible from these experimental data to predict the certainly lethal dose for any undetermined species, for example man, the greater the number of species investigated, the more probable is it that the lethal dose for any undetermined species will be found to lie between the extremes of those investigated. The very similar lethal dose per kilogram in the species studied here makes it probable that the certainly lethal dose of *Pseudechis guttatus* for man is between 0·6 and 1·0 milligramme per kilogram, though these limits are liable to extension with the investigation of further species.

In Queensland deaths reported as due to the bite of the black snake (*Pseudechis porphyriacus*) may actually be caused by the bite of *Pseudechis guttatus*.

There is no evidence from the limited number of observations recorded here that the venom is potent in smaller dosage per kilogram in the larger animals. For the rabbit (average weight two kilograms), guinea-pig (average weight 0·27 kilograms) and for the rat (average weight 0·15 kilograms) it appears to have about the same value, between 0·6 and 0·8 milligramme per kilogram. It is hoped that when further venom is available, the relation of toxicity to body weight of species may be further investigated.

It is a pleasure to acknowledge my indebtedness to Dr. N. H. Fairley who collected the venoms used in these experiments, and to Miss Beryl Splatt who did all the weighings for me.

We are indebted to Mr. Heber A. Longman for his suggestion that the speckled snake described to him was probably *Pseudechis guttatus* (De Vis), which it indeed proved to be.

CONCLUSIONS.

1. The venom of *Pseudechis guttatus* contains thrombase, hæmolysin, hæmorrhagin and neurotoxin.

2. The certainly lethal dose for the guinea-pig, rabbit and rat lies between 0·6 and 0·8 milligramme per kilogram and the subcutaneous-intravenous index is about one.

The certainly lethal dose for the mouse is one milligramme per kilogram by intravenous and 2·5 milligrammes per kilogram by subcutaneous injection. The subcutaneous-intravenous index is 2·5 for this species.

3. The venom is more hæmolytic than that of the tiger snake (*Notechis scutatus*) and has less thrombotic activity in the species investigated than the venoms of *Notechis scutatus* and *Pseudechis porphyriacus*.

4. The pathological changes produced by subcutaneous injection of the venom in small animals, particularly in the guinea-pig, resemble those produced by diphtheria toxin.

5. The venom, like that of other Australian colubrides, has a stimulant action on the isolated plain muscle of the guinea-pig.

REFERENCES.

(1) C. W. De Vis: "Annals of the Queensland Museum," Number VI, 1905, page 49.
(2) L. F. Shackell and W. Williamson: "The Relation of Dosage to Effect," *Journal of Pharmocology and Experimental Therapeutics*, 1924, Volume XXIV, page 53.
(3) J. W. Trevan: "The Error of Determination of Toxicity," *Proceedings of the Royal Society*, S.B., July, 1927, page 483.

CRITERIA FOR DETERMINING THE EFFICACY OF LIGATURE IN SNAKE BITE.

(THE SUBCUTANEOUS-INTRAVENOUS INDEX.[1])

By N. HAMILTON FAIRLEY, O.B.E., M.D., D.Sc., F.R.C.P.,
Walter and Eliza Hall Institute of Research, Melbourne.

Immediate ligature has long constituted one of the recognized measures for adoption in the treatment of snake bite. First practised by Kemper it was subsequently advocated by Felix Fontana who in 1781 published his famous work *"Traité sur le Venin de la Vipère"* in Florence, while holding the appointment of naturalist to the Grand Duke of Tuscany.

In America Weir Mitchell(1) emphasized its value pointing out that it afforded an opportunity for local remedies and for a time secured the system from the consequence of the venom inoculation, but that this was all that could be expected of it. Following Holbrook and Ogier, whose experimental work was never published, he advised intermittent as opposed to continuous ligature. The cord was loosened for a few minutes from time to time and a careful watch was kept for constitutional symptoms the onset of which called for religature without delay.

In Australia Martin(2) found that six to ten times the fatal dose of black snake venom (*Pseudechis porphyriacus*) could be injected into the leg of a rabbit and be followed by little or no constitutional disturbance provided an elastic ligature was applied immediately afterwards above the site of inoculation sufficiently tightly to obliterate the circulation completely for twenty minutes. Ligature under these circumstances was obviously doing much more than temporarily blocking the circulation. Martin noted that œdema occurred in the inoculated limb after removal of the ligature, but not in the ligatured limb of an uninoculated rabbit. He suggested that the combined local influence of the poison and anæmia on the vessel walls resulted in a considerable delay in the absorption of the inoculated venom and that this probably constituted the basis of its beneficial therapeutic action. This classical experiment profoundly influenced the clinical treatment of snake bite in this country.

Later Martin(3) reported similar results with both tiger snake (*Notechis scutatus*) and black snake (*Pseudechis porphyriacus*) venoms and pointed out that on incising the site of inoculation the blood and lymph in the immediate neighbourhood of the seat of inoculation were clotted, so that the poison

[1] This research was carried out under a grant from the Commonwealth Government Department of Health.

was temporarily shut up and could be only slowly absorbed. On repeating his experiments with samples of venom which had been previously heated to 75° C. to destroy their power of producing intravascular clotting, the only result of ligaturing the limb was to prolong the death time. By this ingenious observation Martin showed that the beneficial results of ligature observed in the case of these two Australian colubride venoms were due to the effect on the thermolabile fibrin ferment which they contained.

In the same article Martin and Lamb pointed out that the action of ligature in the case of venoms, such as those of the cobra and the krait which contain no fibrin ferment, is to delay the absorption as long as it may be applied. In those venoms, however, like *Echis carinata* and some of the Australian snakes which contain fibrin ferment, ligature results in the fixation of considerable amounts of venom *in situ* and in consequence sometimes proves a life-saving procedure of great utility. The value of other local remedial measures, especially radical excision of the bitten tissues, was also emphasized.

More recently in India Acton and Knowles[4] gave subcutaneous injections of cobra and Russell's viper venom into the distal part of the hind limbs of rabbits, immediately afterwards applying a ligature for a period of twenty minutes. With cobra venom the onset of death was delayed, the poison being temporarily locked up within the ligatured limb. Its therapeutic value consisted in slightly increasing the time during which antisera and local remedies could be applied. In the case of Russell's viper venom which is rich in thrombase, they found not only that ligature delayed the death time, but by locking up the venom locally and promoting thrombosis it also greatly decreased absorption even after removal of the ligature. It also tended to prevent pulmonary embolism. From a therapeutic point of view the procedure not only lengthened the time within which the administration of systemic remedies might be successful in neutralizing the venom within the general circulation, but in some instances it actually saved life although no other remedy was employed.

In regard to American snakes different authors appear to hold different views concerning its efficacy. Noguchi[5] advocates ligature, whereas Brazil[6] is not favourably impressed, except as an expedient permitting other methods of treatment. In dogs and guinea-pigs Brazil found that ligature even when applied before the inoculation of venom did not prevent its systemic action, the poison being transferred by direct spread through tissue cells and not by the vessels of the region. It also possessed the very real disadvantage with certain species of *Lachesis* of increasing the tendency to gangrene at the site of venom inoculation. Crimmins[7] states that in fifty-eight experiments in dogs inoculated with the anticoagulant venom of the Texas diamond-back rattle snake (*Crotalus adamanteus*) mechanical suction with a breast pump was the only local measure which was effective. The tourniquet *per se* was not a life saving procedure, but as this venom spreads by the lymphatics its absorption was prevented until such time as it could be sucked out by mechanical means.

Investigations on the Australian venoms have mainly been confined to those of the black and tiger snakes, little detailed work having been recorded on death adder and brown snake venoms and none in the case of the copper-head.

In view of these facts and also because of the high mortality reported by Tidswell for death adder and tiger snake bites in man, it was decided to reinvestigate the value of ligature and other remedial measures in the case of the more deadly Australian colubride venoms, larger sized animals such as sheep and goats being utilized for this purpose.

THE ABSORPTION OF VENOM.

In order to appreciate the rationale of ligature it is necessary to visualize what actually is happening in the bitten extremity.

The Australian snakes are short fanged and for this reason their venom is generally injected only into the subcutaneous tissues. Considerable torsion and compression of the soft tissues, however, are produced during the actual bite and where the hands and feet are involved, venom may sometimes be deposited in intramuscular zones or tendon sheaths. It appears but rarely to be injected into the superficial veins. With the death adder, owing to the considerable forward rotation and greater length of the fangs and its powerful bite due to the extremely well developed temporal muscles, deposition of poison into the deeper tissues much more frequently occurs.

When black snake venom was inoculated directly into a vein, Martin[9] showed that death resulted rapidly from intravascular thrombosis and circulatory stasis, but when moderate quantities were injected into the subcutaneous tissues neurological symptoms predominated. Absorption was shown to occur directly into the blood vessels, for after ligature of the lymphatics from the limb and the thoracic duct no delay was found in the onset of symptoms.

The rapidity of absorption is naturally of great practical importance, for on it all rational forms of local treatment must be based. Acton and Knowles[4] injected one hundred milligrammes of cobra venom into the tips of the tails of four dogs weighing nine to thirteen kilograms and anæsthetized with chloroform-ether mixture. The tails were amputated seven and a half centimetres above the site of inoculation at one minute intervals with a single stroke of a sharp axe and all bleeding arrested. All animals died within a period of forty-five to eighty-eight minutes, so that even within sixty seconds a lethal dose had been absorbed. The scarcity of subcutaneous tissue and the vascularity of the periosteum in dogs' tails were regarded as accelerating absorption at the site of injection; the experiment was repeated on monkeys. Ten minimum lethal doses of cobra venom (twenty-four milli-

grammes) were injected subcutaneously into the tails of monkeys which were again amputated at minute intervals. Exactly the same technique was employed except that a smaller dose of venom was given. They found that with this smaller dosage it took about eight minutes for one minimum lethal dose to pass into the general circulation.

During the present investigation I have observed rabbits die within one minute and sheep within fifteen minutes of natural bite by *Notechis scutatus* and the following experiments illustrate the extreme rapidity with which venom may be absorbed from the subcutaneous tissues of the latter animals.

Three sheep, weighing 49·1, 44·5 and 43·6 kilograms, were effectively bitten over the skin of the right thorax by three different tiger snakes. At intervals of two, five and ten minutes respectively a widespread excision of the skin and subcutaneous tissues (five centimetres by five centimetres) over the bitten area right down to the muscles was made and a large Bier's suction glass immediately applied. In each instance after the bite the snake was milked and reserve venom demonstrated.

The animal in which radical excision was postponed for ten minutes, developed symptoms in eleven minutes and died fifteen minutes after the bite was inflicted. Death resulted from portal thrombosis and *ante mortem* clotting of the blood in the right side of the heart and pulmonary arteries.

The second animal became paralysed three hours and thirty-nine minutes after being bitten and died from neurotoxic effects six hours and twelve minutes later, despite the fact that local treatment was carried out within five minutes. Severe hæmorrhage from the site of the excision subsequently developed, a complication which was no doubt related to the negative phase of lessened coagulability of the blood produced by tiger snake venom. Death in this instance may have been accelerated by the resulting exsanguination.

In the third sheep a complete excision down to the muscular layer was made within two and a half minutes, the operation commencing two minutes after the bite. Paralysis developed in thirty-six hours and fifty-six minutes and death resulted in sixty-four hours. Locally there was congestion and hæmorrhage of the muscles surrounding the area of the excision and spreading gelatinous œdema in the deep tissues covering the chest wall. The lungs, liver, small intestines, thyreoid, thymus and pancreas contained hæmorrhages, while the kidneys were severely congested. The right side of the heart was dilated and flabby and filled with *post mortem* clot. Local measures in this instance almost proved successful, as indicated by the long latent period preceding the onset of paralysis and the prolonged death time.

The results of these experiments show that the absorption time for a lethal dose of tiger snake venom in a large animal like the sheep may be less than two and a half minutes when it is naturally bitten and other results indicate that it does not exceed two minutes in an effective bite from an averaged sized tiger snake. Absorption commences at the instant of injection and the actual absorption time is dependent on the size and susceptibility of the animal bitten, the vascularity of the tissues at the site of the bite and the quality and quantity of venom injected.

The size of the dose is all important and when smaller amounts of tiger snake venom (such as two certainly lethal doses) were injected, I found local measures such as radical excision and suction effective even in the absence of ligature when applied within five minutes of the injection. In the experiments detailed in this paper ligature was generally applied within a quarter to one minute and never more than two minutes after the subcutaneous inoculation of venom the dosage of which rarely exceeded two certainly lethal doses. Cessation of the circulation was thus established a considerable time before a lethal dose could have been absorbed.

Application of the Ligature.

From the preceding observations it is evident that if ligature or any other local mode of therapy is to be effective, such measures must be instituted immediately after the bite, every minute being a matter of supreme importance to the patient.

The next point to consider is the site of application of the ligature. In the upper or lower extremity it must be applied on the heart side of the bite over a single bone, that is on the arm or thigh, and in addition in the case of finger and toe bites a ligature may be placed at the base of the implicated digit. The application of a tourniquet to the forearm and leg is futile owing to the impossibility of effectively compressing the interosseous vessels where two bones are present.

Complete circulatory stasis is to be aimed at and pressure must be sufficiently severe to compress the arteries as well as the veins of the limb. Thick rubber tubing (15·8 millimetres in diameter) makes an excellent tourniquet, but as a first aid measure strips of clothing can be utilized if loosely applied and susequently tightened by twisting with a stick inserted under the knotted junction.

Intermittent and Continuous Ligatures.

Generally it is advised not to leave on a ligature for more than twenty minutes on account of the danger of gangrene to the limb. This is especially the case with viperine venoms whose contents in thrombase, cytolysins and bacteria are such that suppuration, ulceration and gangrene are not infrequently observed even where ligature has not been applied at all. The suggestion of Weir Mitchell, Martin and others of temporarily flooding the limb with blood and subsequently reapplying the ligature has much to be said in its favour. For rattlesnake bites Crimmins[7] advocates loosening the tourniquet every twenty minutes for five seconds in order to reestablish the circulation and continuing this process until the patient reaches the doctor. The value of such a procedure is dependent on the more prolonged localization of the venom in

the bitten extremity and not on any protective immunity response caused by the gradual liberation of poison as suggested recently by MacInnes.[10]

With the colubride snakes the ligature time can be safely extended to a single period of half an hour or even longer and in the present series of experiments thirty to thirty-five minutes was generally adopted. This time was ten to fifteen minutes longer than Martin adopted in his ligature experiments on rabbits.

In sheep intermittent ligature up to a period of two hours proved no more efficacious than continuous ligature for thirty minutes and three animals which were inoculated with two, one and a half and one minimum lethal doses of tiger snake venom subcutaneously died in 6·8, 7·6 and 30·7 hours respectively despite the former procedure. During these experiments I noted that removal of the ligature for a period of five seconds was not sufficient to restart bleeding in incised wounds below the level of the ligature and it is questionable if this interval which is so universally advocated, is sufficiently prolonged to reestablish the circulation effectively under such circumstances.

Outline of Methods Adopted.

The general procedure was first to estimate the approximate certainly lethal dose of venom for the particular species of animal to be experimented on in terms of milligrammes per kilogram of body weight. This was done by injecting subcutaneously increasing quantities of dried venom, the actual amounts used being detailed in the various tables dealing with this question. Owing to the use of large and expensive animals their number naturally had to be limited and it is possible that in some instances underestimates of the certainly lethal dose have been made. The practical effect of such an underestimation in ligature experiments would operate favourably as far as the interpretation of its efficacy was concerned, but a perusal of tabulated results does not suggest the existence of such a state of affairs.

In the ligature experiments the venom was injected into the subcutaneous tissues of the right foreleg in the vicinity of the metacarpo-phalangeal articulation and a rubber tourniquet of not less than 12·5 millimetres diameter was applied on the stretch to the single metacarpal bone, several turns being made round the limb before it was finally knotted. A small incision was then made below to ascertain if the circulation had ceased and this was repeated just before the ligature was removed in order to make sure that it was still effective. Generally dried venom appropriately diluted with saline solution was employed, one to four certainly lethal doses being contained in one cubic centimetre, but in some instances minute amounts of freshly collected undiluted fluid venom were utilized in order to determine whether dilution of thrombase was preventing thrombosis developing locally and so affecting the efficacy of ligature as a therapeutic procedure.

Finally for reasons which will be stated later the intravenous certainly lethal dose was also determined and the subcutaneous-intravenous index[1] calculated.

TABLE I.

Observations on the Certainly Lethal Dose of Tiger Snake Venom (Notechis scutatus) in Sheep.

Identification Number.	Weight in Kilograms.	Total Dosage in Milligrammes.	Dosage in Milligramme per Kilogram Body Weight.	Result.		
				Recovered.	Onset of Paralysis.	Death Time.
					Hours. Minutes.	Hours. Minutes.
33	44·2	0·09	0·002	Yes	—	—
31	37·5	0·11	0·003	Yes	—	—
5	37·5	0·15	0·004	Yes	—	—
4	34·0	0·17	0·005	Yes	Yes	—
35	43·6	0·25	0·006	No	22 30	49 45
7	44·2	0·26	0·006	Yes	—	—
45	35·45	0·25	0·007	Yes	—	—
44	50·0	0·35	0·007	No	10 0	23 30
46	44·5	0·36	0·008	Yes	Yes	—
47	33·6	0·27	0·008	Yes	—	—
36	31·5	0·25	0·008	No	14 10	45 15
48	35·0	0·31	0·009	No	21 40	23 10
4	34·8	0·35	0·010[1]	No	10 27	19 57
37	35·1	0·5	0·014	No	6 40	8 10
41	30·1	0·75	0·025	No	6 35	7 20
9	32·4	1·0	0·031	No	Yes	4 50
8	50·0	10·0	0·20	No	Yes	0 15
96	54·5	27·2	0·50	No	1 4	1 40

[1] 0·01 milligramme per kilogram was the certainly lethal dose.
Animal No. 4 had survived 0·17 milligramme of tiger snake venom thirty-two days previously.

Experiments with Tiger Snake Venom in Sheep.

Forty-five sheep were utilized for these particular experiments which will be discussed below.

The Certainly Lethal Dose on Subcutaneous Injection.

Observations regarding the subcutaneous certainly lethal dose of tiger snake venom for sheep are detailed in Table I. Seventeen sheep varying in weight from 30·1 to 50·0 kilograms were used. One animal, No. 4 (*a*), was twice injected, receiving on the first occasion 0·17 milligramme from which it recovered, and thirty-two days later double this

[1] I suggest the use of this term in order to avoid more cumbersome phraseology. It is determined for each species of animal by dividing the subcutaneous by the intravenous certainly lethal dose expressed in milligrammes per kilogram of body weight.

dosage which proved fatal. Deaths were not observed until quantities of venom equalling 0·005 milligramme per kilogram were exceeded and two out of three animals survived 0·008 milligramme per kilogram. With dosages of from 0·009 milligramme per kilogram onwards fatal results invariably followed and in consequence the approximate certainly lethal dose was taken as 0·01 milligramme per kilogram of body weight. Generally the venom was diluted with saline solution so that one cubic centimetre contained 0·5 milligramme, but when many lethal doses were used it was ten times this strength (that is five milligrammes were contained in one cubic centimetre).

TABLE II.

Ligature Experiments in Sheep inoculated subcutaneously with Tiger Snake Venom.

Identification Number.	Weight in Kilograms.	Total Dosage in Milligrammes.	Dosage in Milligramme per Kilogram.	Number of Certainly Lethal Doses.	Ligature.		Result.			
					When Applied.	Duration	Paralytic Time.		Death Time.	
						Minutes.	Hours.	Minutes.	Hours.	Minutes.
5	34·7	0·35	0·01	1	2 minutes	34	14	44	19	14
70	46·3	0·46	0·01	1	1 minute	35	15	0	20	20
95	46·4	0·46	0·01	1	Few seconds	35	25	30	28	57
88	46·8	0·47	0·01	1	Few seconds	35	15	30	20	30
34	41·4	0·52	0·0125	1¼	1 minute	35	6	43	13	7
31	33·9	0·52	0·015	1½	2 minutes	30	—		27	2
32	41·6	0·73	0·0175	1¾	1 minute	35	9	54	12	16
54	43·2	0·86	0·02	2	Before	30	—		27	2
50	43·4	1·52	0·035	3½	Before	30	6	17	9	37

All the animals died.
Animal No. 5 had survived 0·15 milligramme of tiger snake venom thirty-two days previously.

The eight animals succumbing to 0·25 to 0·10 milligramme of venom all died from neurotoxic effects, a result which invariably followed when only small multiples of the lethal dose were employed. Sheep No. 8, however, which received twenty certainly lethal doses (ten milligrammes) died in fifteen minutes with *ante mortem* clotting of the blood in the right auricle and ventricle and pulmonary arteries. The portal vein was also thrombosed.

It might be noted that though the last sheep, No. 96, received a much larger quantity of venom, it died in one hour and forty minutes with bulbar paralysis, thrombase effects not being in evidence. Similar individual variations in susceptibility to thrombase were also noted in sheep effectively bitten by *Notechis scutatus* when many lethal doses must inevitably have been injected into the subcutaneous tissues.

Ligature Experiments with Dried and Fresh Venom.

Taking 0·01 milligramme per kilogram as the certainly lethal dose thirteen sheep were injected subcutaneously with from one to three and a half lethal doses (see Table II). Ligature was applied for a period of from thirty to thirty-five minutes as indicated in the table and in two instances complete stasis of the circulation was produced prior to the injection. In the case of the other sheep it was applied within a period varying from a few seconds to two minutes. All the animals developed paralysis of the limbs and bulbar centres and died of respiratory failure in a period of from nine hours and thirty-seven minutes to twenty-eight hours and fifty-seven minutes. No appreciable lengthening of the death time was noted except perhaps in the case of those receiving two and three and a half certainly lethal doses. Sheep No. 5 (*a*) had survived 0·15 milligramme of tiger snake venom some thirty-two days previously, but it evidently had developed no immunity, for despite ligature for thirty-four minutes applied within two minutes of the injection death resulted.

These results were most unexpected, indicating as they did that ligature was not a life-saving procedure as far as tiger snake venom inoculations in sheep were concerned. It was, therefore, decided to inject a series of ovines with a known volume of fresh pooled tiger snake venom in order to ascertain whether dilution with saline solution could possibly induce weakening or masking of the thrombotic action of thrombase in the subcutaneous tissues.

After drying, the total solids contained in one cubic centimetre of the pooled fresh venom were determined in order to ascertain the number of certainly lethal doses present in the dried residue.

A quantity of 0·01 cubic centimetre of undiluted venom was regarded as the minimum amount that could be delivered into the subcutaneous tissues with any degree of accuracy and this was the amount generally utilized.

In the first experiment (Table III) three sheep each weighing 44·5 kilograms were selected and injected subcutaneously with 0·01 cubic centimetre of venom. This amount was estimated to contain two milligrammes, that is 4·5 minimum lethal doses. Ligature was immediately applied for thirty-five minutes in the case of two animals (Nos. 101 and 103), while the third (No. 99) was kept as a control. The latter died in four hours and the two ligatured animals in four hours and thirty-four minutes and seven hours and forty-three minutes respectively.

In the second experiment (Table III)three sheep weighing 45·5 kilograms each received 0·01 cubic centimetre of fresh venom containing 1·86 milligrammes, that is 4·1 certainly lethal doses, while

Table III.

Ligature in Sheep inoculated subcutaneously with Fresh Tiger Snake Venom.

Identification Number.	Weight in Kilograms.	Fluid Venom Injected (Cubic (Centimetre).	Number of Certainly Lethal Doses.	Calculated Weight of Dry Venom (Milligrammes).	Time of Ligature.	Result.		1 Cubic Centimetre of Fluid Venom Dried (Milligrammes).
						Paralytic Time.	Death Time.	
						Hours. Minutes.	Hours. Minutes.	
99	44·5	0·01	4·5	2·0	Control	3 5	4 0	201·1
103	44·5	0·01	4·5	2·0	35 minutes	4 0	4 34	
101	44·5	0·01	4·5	2·0	35 minutes	7 23	7 43	
130	45·5	0·01	4·1	1·86	Control	3 29	3 59	186·1
119	45·5	0·01	4·1	1·86	35 minutes	3 45	3 58	
132	45·5	0·01	4·1	1·86	35 minutes	4 50	5 2	
129	45·0	0·02	8·3	3·72	35 minutes	6 10	7 3	

All animals whether ligatured or not succumbed.

the fourth, a sheep of 45 kilograms, received 0·02 cubic centimetre. Animal No. 130 was used as a control and the others were immediately ligatured for a period of thirty-five minutes. The control died in three hours and fifty-nine minutes and No. 119 in three hours fifty-eight minutes. The other two animals (Nos. 132 and 129) died in five hours two minutes and seven hours three minutes respectively. The last sheep (No. 129) took the longest time to die despite the fact that it had received twice as much venom as the other three sheep. Such a result might be attributed either to the effects of ligature or to natural variation in venom susceptibility. In the case of the other two animals ligature appeared to exert practically no influence on the death time.

The consistently disappointing results obtained in these two experiments (Table III) with undiluted fresh fluid venom taken in conjunction with those obtained with dry venom (Table II) diluted with saline solution show conclusively the ineffectiveness of ligature in sheep inoculated with the venom of *Notechis scutatus*.

The Certainly Lethal Dose on Intravenous Injection.

Observations were also made to determine the approximate certainly lethal dose of tiger snake venom injected into the jugular vein. Thirteen sheep were used for this purpose, the quantity of venom varying from 0·001 to 0·02 milligramme per kilogram of body weight. Death from portal thrombosis occurred irregularly with doses of from 0·002 to 0·004 milligramme per kilogram. All animals injected with 0·005 milligramme per kilogram or larger amounts succumbed in from twelve to one hundred and five minutes (see Table IV) as a result of portal thrombosis or of intracardiac thrombi in the right auricle and ventricle. The latter condition occurred in four sheep and was invariably associated with portal thrombosis. The intravenous certainly lethal dose was estimated at 0·005 milligramme per kilogram, though in sheep specially susceptible to thrombase death followed the injection of even 0·002 milligramme per kilogram.

Experiments with Tiger Snake Venom in Goats.

A limited series of observations was next made on goats in order to ascertain whether ligature in the case of these animals was any more effective.

The Subcutaneous Certainly Lethal Dose.

Seven goats varying in weight from 21·8 to 47·3 kilograms were used for this experiment (see Table V), two of the animals being inoculated twice. Injections of 0·01 milligramme per kilogram caused neurological features such as muscular tremors and ataxia, but paralysis did not occur. One out of three animals receiving 0·015 milligramme per

Table IV.

The Intravenous Injection of Dried Tiger Snake Venom (Notechis scutatus) into Sheep.

Identification Number of Sheep.	Weight in Kilograms.	Total Dosage in Milligramme.	Dosage in Milligramme per Kilogram Body Weight.	Result of Injection.			
				Collapse.	Death Time.	*Ante mortem* Thrombosis.	
						Right Side of Heart.	Portal Vein
				Minutes.	Hours. Minutes.		
92	49·1	0·05	0·001	—	R.	–	–
107	52·7	0·08	0·0015	—	R.	–	–
165	29·5	0·059	0·002	4	1 13	0	+
116	38·2	0·114	0·003	6	R.	–	–
91	53·2	0·16	0·003	—	R.	–	–
111	38·2	0·153	0·004	—	4 0	0	+
114	46·1	0·18	0·004	—	R.	–	–
180	36·4	0·18	0·005	At once	4 27	0	+
61	41·8	0·21	0·005	38	1 45	0	+
118	38·2	0·29	0·0075	2	0 23	+	+
104	52·3	0·39	0·0075	2	0 12	+	+
90	35·5	0·35	0·01	—	0 20	+	+
134	42·7	0·85	0·02	2	0 23	+	+

The venom used varied in strength from 0·1 to 1·0 milligramme in 1 cubic centimetre.
R. indicates that the animal recovered.

kilogram died, while those injected with 0·018 to 0·023 milligramme per kilogram all succumbed after the development of paralysis of the limbs and glosso-pharyngeal muscles. The approximate certainly lethal dose for goats was estimated as 0·18 milligramme per kilogram body weight.

Ligature Experiments.

Six goats were injected with from one to two and a half certainly lethal doses of tiger snake venom into the subcutaneous tissues near the metacarpo-phalangeal joint and a ligature was applied one minute later over the metacarpal bone of the fore limb exactly as in the case of sheep. It was left on for a period of thirty to thirty-five minutes. All animals developed paralysis and died twelve hours and twelve minutes to twenty hours and fifty-five minutes later (see Table VI).

Ligature exerted no beneficial influence in this series of experimental inoculations and as in the case of sheep the indications are that *per se* it is not a life-saving procedure.

The Intravenous Certainly Lethal Dose.

Intravenous injections were given to ten goats, the animals receiving from 0·0009 to 0·018 milligramme per kilogram of body weight. The first five animals receiving up to 0·003 milligramme per kilogram all recovered, but the last five which were given from 0·004 to 0·018 milligramme per

TABLE V.

Observations on the Certainly Lethal Dose of Dried Tiger Snake Venom (Notechis scutatus) injected into the Subcutaneous Tissues of the Goat.

	Number of Goat.	Weight in Kilograms.	Total Venom Injected (Milligrammes).	Dosage in Milligramme per Kilogram Body Weight.	Result.			
					Recovery.	Neurological Symptoms.	Paralytic Time.	Death Time.
							Hours. Minutes.	Hours. Minutes.
1	30	47·3	0·5	0·011	Yes	Yes	—	—
2	14	33·6	0·34	0·010	Yes	Yes	—	—
3	14 (*a*)	31·8	0·48	0·015	Yes	Yes	—	—
4	27	30·0	0·45	0·015	No	Yes	N.R.	20 5
5	56	33·6	0·5	0·015	Yes	Yes	—	—
6	20	21·8	0·39	0·018[1]	No	Yes	18 12	22 7
7	55	37·7	0·75	0·020	No	Yes	10 36	14 51
8	30 (*a*)	47·3	1·0	0·021	No	Yes	N.R.	30 10
9	26	N.R.	5·0	N.R.	No	Yes	N.R.	0 20

[1] The approximate certainly lethal dose was taken as 0·018 milligramme per kilogram body weight.
The injected venom varied in strength from 0·5 milligramme to 2·0 milligrammes per cubic centimetre, except in the case of goat No. 26, which received 5 milligrammes per cubic centimetre.

TABLE VI.

Ligature Experiments on Goats inoculated with Tiger Snake Venom.

Number.	Weight in Kilograms.	Total Dosage in Milligrammes.	Dosage in Milligramme per Kilogram.	Number of Certainly Lethal Doses.	Duration of Ligature.	Result.		
						Recovered.	Paralysed.	Death Time.
					Minutes.		Hours. Minutes.	Hours. Minutes.
57	21·8	0·39	0·018	1·0	35	No	16 20	18 30
59	36·6	0·73	0·02	1·1	30	No	10 25	14 14
17	15·7	0·31	0·02	1·1	35	No	Yes	18 25
60	30·0	0·75	0·025	1·4	35	No	18 15	21 55
42	40·7	1·22	0·03	1·7	30	No	11 0	14 57
58	27·27	1·23	0·045	2·5	35	No	10 20	12 12

The ligature on each occasion was applied one minute after the injection of venom, which was so diluted with saline solution that 1 cubic centimetre contained 2 milligrammes.

TABLE VI (*a*).

Observations on the Certainly Lethal Dose of Dried Tiger Snake Venom (Notechis scutatus) in Goats injected intravenously into Sheep.

Identification Number.	Weight in Kilograms.	Total Dosage in Milligramme.	Dosage in Milligramme per Kilogram Body Weight.	Result.				
				Collapse.	Death Time.	*Ante mortem* Thrombosis.		
						Portal System.	Pulmonary Vessels.	Right Heart.
				Minutes.				
98[1]	16·4	0·015	0·0009	—	—	−	−	−
97[1]	19·1	0·034	0·0018	—	—	−	−	−
99	21·4	0·048	0·00225	—	—	−	−	−
96[1]	27·3	0·082	0·003	10	—	−	−	−
101[1]	25·0	0·075	0·003	5	—	−	−	−
102	35·5	0·142	0·004	3	10	+	+	+
100	21·4	0·13	0·006	N.R.	11	+	+	+
15	20·9	0·25	0·012	2	11	+	+	+
10	14·8	0·21	0·014	1·5	7	+	+	+
56	28·9	0·52	0·018	1·0	4	+	+	+

[1] These animals were injected with a solution containing 0·1 milligramme per cubic centimetre, while the remainder were injected with one containing 1·0 milligramme per cubic centimetre.
[2] The blood in the inferior *vena cava* was clotted in this animal; in all others it was fluid.

kilogram, succumbed from intravascular thrombosis involving the pulmonary and portal systems as well as the right heart (see Table VI (*a*)). In only one animal (No. 56) which received the maximum dosage, was *ante mortem* thrombosis of the inferior *vena cava* observed. These findings indicate that the intravenous certainly lethal dose is 0·004 milligramme per kilogram and as the subcutaneous certainly lethal dose is 0·018 milligramme it follows that the subcutaneous-intravenous index in goats is 4·5. Thus while the intravenous certainly lethal dose in sheep and goats is approximately equal, the sheep is about twice as susceptible to venom given subcutaneously.

The clinical syndrome following intravenous injection in these animals is interesting. Within two minutes they almost invariably become restless, micturate, defæcate and develope muscular tremor and a variable grade of dyspnœa. Complete collapse may or may not follow and in some instances, even where recovery ensues, the respirations are uncountable. In fatal cases dyspnœa is always severe and circulatory collapse extreme, while pallor of the mucous membranes, stiffness of the muscles, head retraction, spasmodic extensor kicking movements and twitching of the ears and skin are characteristic. The pupils become dilated and insensitive to light, but no other neurological features are noted. Death occurred always within eleven minutes from intracardiac thrombosis.

Similar circulatory collapse is seen in sheep after the injection of both tiger snake and Russell's viper venoms and the rapidity with which it developes and passes off in animals which recover, suggests that acute vasomotor failure underlies the condition.

Experiments with Death Adder Venom in Sheep.

The constituents and physiological effects of death adder venom have been scantily studied and no observations exist regarding the efficacy of ligature in death adder bites following the injection of this venom into the subcutaneous tissues of experimentally inoculated animals. Sheep which have been naturally bitten, injected intravenously or inoculated subcutaneously with large doses of this venom die without evidence of intravascular thrombosis appearing, while observations on the blood after intravenous injections entirely fail to show any decrease in the coagulation time such as is observed within the first few minutes following similar injections with tiger snake or Russell's viper venom in these animals. Indeed the only effect observed is a transient increase in the coagulation time. This, as in the case of cobra venom, may be due to the presence of anticoagulins.

Portal thrombosis and intracardiac *ante mortem* thrombi were never met with at autopsy and the data which I have collected during the present investigation, indicate that thrombase is definitely absent from death adder venom. These observations are of considerable biological interest for in many of its external characteristics *Ancanthophis antarcticus* is more closely related to the *Viperidæ* than either *Notechis scutatus* and *Pseudechis porphyriacus* both of which are typical colubrides. The venom, however, of the latter two snakes has been shown by Martin to be rich in thrombase and for this reason its absence in the death adder was unexpected.

The Certainly Lethal Dose on Subcutaneous Injection.

In determining the certainly lethal dose eleven sheep were utilized. They received quantities of death adder venom varying from 0·01 to 0·06 milligramme per kilogram of body weight. The results are tabulated in Table VII. It will be noted that all animals inoculated with doses up to 0·2 milligramme per kilogram survived with one exception (No. 68), whereas all died when 0·25 milligramme per kilogram or larger quantities were injected. No. 67 (*a*) died when 0·0275 milligramme per kilogram was given, but five days previously it had survived 0·2 milligramme per kilogram without paralytic features supervening. For purposes of ligature experiments the certainly lethal dose was taken as 0·025 milligramme per kilogram.

Ligature Experiments with Dried and Fresh Venom.

In the first experiment four sheep varying in weight from 43·8 to 57·3 kilograms were inoculated with dried death adder venom appropriately diluted with saline solution, the amount injected varying from one to 2·4 certainly lethal doses. Ligature was

TABLE VII.

Observations on the Certainly Lethal Dose of Dried Death Adder Venom (Ancanthophis antarcticus) injected subcutaneously into Sheep.

Identification Number.	Weight in Kilograms.	Total Dosage in Milligrammes.	Dosage in Milligramme per Kilogram Body Weight.	Result.		
				Recovered.	Paralytic Time.	Death Time.
					Hours. Minutes.	Hours. Minutes
33	45·9	0·46	0·01	Yes	—	—
34	41·4	0·62	0·015	Yes	—	—
32	41·4	0·62	0·015	Yes	—	—
68	38·2	0·69	0·018	No	Yes	36 6
67	44·3	0·88	0·02	Yes	—	—
65	44·3	0·88	0·02	Yes	—	—
121	46·8	1·17	0·025[1]	No	44 40	45 35
63	43·9	1·1	0·025	No	27 30	28 40
67	44·3	1·22	0·0275	No	7 34	14 36
45	33·6	1·0	0·03	No	6 7	11 4
47	35·0	2·0	0·057	No	2 45	4 42
46	42·5	2·55	0·06	No	2 14	4 8

The strength of the venoms used varied between 2 and 4 milligrammes in 1 cubic centimetre.
[1] The certainly lethal dose was regarded as being approximately 0·025 milligramme per kilogram.
Animal No. 67 had received 0·02 milligramme per kilogram five days previously without paralysis developing.

applied immediately and was left on for thirty-five minutes. The results are incorporated in Table VIII, a perusal of which shows that all animals became paralysed and later succumbed to the neurotoxic effects of the poison.

A second experiment was then performed, freshly collected pooled venom being used, one cubic centimetre of which was found to contain 282·5 milligrammes after drying in a desiccator under negative pressure.

TABLE VIII.

The Effect of Immediate Ligature in Sheep inoculated subcutaneously with Dried Death Adder Venom (Ancanthophis antarcticus).

Identification Number.	Weight in Kilograms.	Total Dosage in Milligrammes.	Dosage in Milligramme per Kilogram Body Weight.	Number of Certainly Lethal Doses.	Result.	
					Paralytic Time.	Death Time.
					Hours. Minutes.	Hours. Minutes.
69	43·86	1·1	0·025	1·0	15 18	44 22
65	44·3	1·2	0·027	1·1	16 49	21 58
51	44·5	1·3	0·029	1·2	10 15	11 58
52	57·3	3·4	0·059	2·4	2 0	5 14

The strength of the venom used varied between 2 and 4 milligrammes in 1 cubic centimetre.
All cases terminated fatally; ligature was applied immediately and left on for thirty-five minutes.

Two sheep weighing 48·2 and 48·5 kilograms were injected with 0·01 cubic centimetre (2·3 certainly lethal doses) of fluid venom and immediately afterwards ligature was applied for thirty-five minutes in the case of the second animal (No. 76), the first acting as a control.

The next two animals which weighed 43·9 kilograms were each given 0·02 cubic centimetre (5·1 certainly lethal doses) of venom and No. 81 was ligatured immediately for fifty minutes. Injections were repeated with Numbers 82 and 87 when 0·03 cubic centimetres (7·1 certainly lethal doses) of venom were given. The latter animal was ligatured for fifty minutes, while the former acted as the control. The results are detailed in Table IX. All six animals succumbed and the variations in their death time are so insignificant that ligature is obviously holding up the venom in the limb only as long as it is applied. The results obtained both with fresh and dried venom are in keeping with the findings of observers regarding ligature experiments with colubride snakes in other parts of the world, whose venom contains no thrombase.

The Certainly Lethal Dose on Intravenous Injection.

A series of injections was also given into the jugular vein of eight sheep in order to estimate approximately the certainly lethal dose of death adder venom. The results are incorporated in Table X, an examination of which shows that both animals receiving 0·025 milligramme per kilogram which was the estimated certainly lethal dose for subcutaneous injection, recovered. This finding may possibly be due to the fact that the subcutaneous certainly lethal dose has been underestimated owing to the limited number of animals on which it was determined. On the other hand when venom is rapidly introduced into the blood stream, it may be that some mechanism comes into play whereby a part of it is excreted or destroyed before linkage to nervous tissue has time to occur.

Whichever explanation holds, it is at least certain that death adder venom is no more potent when introduced intravenously than by the subcutaneous route, while actual calculations show that the subcutaneous-intravenous index is less than unity. This finding taken in conjunction with other data constitutes strong evidence regarding the absence of thrombase from death adder venom.

Experiments with Copper-head Venom in Sheep.

The various constituents present in Australian copper-head venom (*Denisonia superba*) have never been previously studied and no observations exist with regard to the effects of ligature either from the clinical or the experimental points of view.

In a preliminary series of unpublished observations on the physiological effects of this venom in small laboratory animals, Kellaway at this institute failed to demonstrate evidence of thrombase and concluded that lethal effects were essentially due to neurotoxin, no matter by which route the venom was introduced. Later working on sheep I obtained similar results, and even after the injection

TABLE IX.

Ligature Experiments in Sheep inoculated subcutaneously with Fresh Death Adder Venom (Ancanthophis antarcticus).
(1 cubic centimetre = 282·5 milligrammes Dried Venom.)

Identification Number.	Weight in Kilograms.	Quantity of Fresh Venom (Cubic Centimetre).	Time of Ligature.	Number of Certainly Lethal Doses.	Result.	
					Paralytic Time.	Death Time.
					Hours. Minutes.	Hours. Minutes.
86	48·2	0·01	Control	2·3	5 21	8 5
76	48·5	0·01	50 minutes	2·3	4 0	5 42
78	43·9	0·02	Control	5·1	1 34	1 59
81	43·9	0·02	35 minutes	5·1	3 5	3 51
82	47·3	0·03	Control	7·1	1 22	1 40
87	47·5	0·03	35 minutes	7·1	2 9	2 38

The ligature was applied immediately after the injection and kept on for thirty-five minutes in animals Nos. 81 and 87 and for fifty minutes in animal No. 76.

TABLE X.

The Intravenous Injections of Death Adder Venom (Ancanthophis antarcticus) in Sheep.

Identification Number.	Weight in Kilograms.	Total Dosage in Milligrammes.	Dosage in Milligramme per Kilogram Body Weight.	Result.			Cause of Death.	
				Recovered.	Paralytic Time.	Death Time.	Neurotoxic.	Intravascular Thrombosis.
					Hours. Minutes.	Hours. Minutes.		
100	47·3	0·95	0·02	Yes	—	—	—	—
80	37·7	0·94	0·025	Yes	—	—	—	—
128	44·5	1·11	0·025	Yes	—	—	—	—
120	43·6	1·2	0·028	No	5 10	19 40	Yes	No
125	44·5	1·34	0·03	No	26 28	29 3	Yes	No
97	52·7	2·64	0·05	No	1 36	4 51	Yes	No
131	44·5	4·45	0·10	No	0 41	1 12	Yes	No
105	40·5	8·1	0·20	No	0 19	0 28	Yes	No

In both animals Nos. 131 and 105 all the vessels contained fluid blood.
The strength of the venom varied between 2 and 5 milligrammes in 1 cubic centimetre.

of several minimum lethal doses of this venom into the jugular vein these animals die without any evidence of *ante mortem* thrombosis involving the portal system, the pulmonary arteries or the right auricle and ventricle. Furthermore, the coagulability of the blood immediately after such injections is not increased as in the case with the thrombase containing venoms. On the contrary curves obtained by plotting out the coagulation times showed a definite retardation in the clotting power of the blood, a result which is evidently produced by anticoagulins which are commonly represented in the other colubride venoms.

The Certainly Lethal Dose on Subcutaneous Injection.

In estimating the certainly lethal dose of dried copper-head venom a series of twelve observations on eight sheep were made, Nos. 62 (*a*), 66 (*a*), 71 (*a*) and 74 (*a*) each receiving a second injection five days after the initial one had been given. Only small doses of venom (0·01 to 0·04 milligramme per kilogram) were injected on the first occasion (see Table XI).

The use of animals which have once been injected, cannot be regarded as a sound procedure and if further supplies of venom had been available, another series of sheep would have been injected. It is unlikely, however, that within five days any protection from antibody production would have resulted. Another possibility is that the animals may not have recovered completely from the toxic effects of the first injection and in consequence may succumb to what normally would constitute a sublethal dose of venom. In point of fact, however, data obtained from a fresh series of animals during ligature experiments did not indicate that any gross underestimation of the subcutaneous certainly lethal dose had resulted from this cause.

An examination of the results contained in Table XI shows that animals receiving 0·01 to 0·07 milligramme per kilogram invariably recovered, though two were temporarily paralysed, while those receiving 0·1 to 0·3 milligramme invariably died. Both sheep injected with 0·1 milligramme per kilogram succumbed and this quantity was provisionally taken as the certainly lethal dose for subcutaneous injections.

Ligature Experiments with Dried Venom.

Six sheep were used in ligature experiments, the animals receiving from one to one and a half certainly lethal doses of dried venom appropriately diluted with saline solution. Immediately after the injection a tight ligature was applied for a continuous period of thirty-five minutes. The results are incorporated in Table XII and show that five out of six animals died irrespective of ligature. One sheep (No. 116) survived after being completely paralysed for a period of two days, a result which might be attributed to the beneficial effects of

TABLE XI.

Observations on the Certainly Lethal Dose of Dried Copper-head Venom (Denisonia superba) injected subcutaneously into Sheep.

Identification Number.	Weight in Kilograms.	Total Dosage in Milligrammes.	Dosage in Milligramme per Kilogram Body Weight.	Result.		
				Recovery.	Paralytic Time.	Death Time.
					Hours. Minutes.	Hours. Minutes.
66	45·5	0·45	0·01	Yes	—	—
71	46·8	0·94	0·02	Yes	—	—
74	46·4	1·39	0·03	Yes	—	—
70	46·4	1·39	0·03	Yes	24 0	—
62	47·5	1·9	0·04	Yes	—	—
64	44·5	3·11	0·07	Yes	18 33	—
102	45·7	4·57	0·10	No	7 42	24 14
66 (*a*)	45·5	4·55	0·10	No	6 25	25 42
84	45·9	5·73	0·125	No	4 5	7 51
62 (*a*)	47·5	7·13	0·15	No	2 27	4 41
71 (*a*)	46·8	9·36	0·20	No	2 41	5 34
74 (*a*)	46·4	13·9	0·30	No	2 17	3 13

The certainly lethal dose was taken as 0·1 milligramme per kilogram body weight.
The strength of the solution of venom used was 1 cubic centimetre = 2 milligrammes for smaller doses and 1 cubic centimetre = 10 milligrammes for the larger ones.

TABLE XII.

The Effect of Immediate Ligature for Thirty-five Minutes in Sheep inoculated subcutaneously with Copper-head Venom (Denisonia superba).

Identification Number.	Weight in Kilograms.	Total Dosage in Milligrammes.	Dosage in Milligramme per Kilogram Body Weight.	Number of Certainly Lethal Doses.	Result.		
					Recovered.	Paralytic Time.	Death Time.
						Hours. Minutes.	Hours. Minutes.
115	45·4	4·5	0·10	1[1]	No	7 38	17 3
116	46·8	4·7	0·10	1	Yes; after two days' paralysis	12 7	—
85	45·7	5·7	0·125	1¼	No	9 52	15 5
94	45·9	5·7	0·125	1¼	No	7 6	9 12
77	45·8	5·7	0·125	1¼	No	7 27	9 25
127	46·8	7·0	0·15	1½	No	8 33	57 43

[1] The strength of the venom was 1 cubic centimetre = 2 milligrammes; in all the others it was 1 cubic centimetre = 10 milligrammes.

ligature, but which is more likely to be dependent on high powers of natural resistance.

As already emphasized, considerable variations in individual susceptibility are found in any given species of animals and it is necessary in consequence to use a much larger series than has been practicable with sheep in order to ascertain the absolute upper limit of the certainly lethal dose. Only approximate determinations of this figure are possible with such costly animals as sheep and in this instance it is possible that 0·1 milligramme per kilogram really constituted a sublethal rather than a lethal dose for the sheep in question (No. 116). Six out of seven animals referred to in Tables XI and XII were killed with doses of 0·1 to 0·125 milligramme per kilogram on subcutaneous injection. This fact taken in conjunction with the grave condition produced in the only animal (No. 116) recovering from the injection of 0·1 milligramme per kilogram, indicates that in any case this figure must closely approximate to the absolute certainly lethal dose as far as subcutaneous injections are concerned.

The Certainly Lethal Dose on Intravenous Injection.

Ten animals were injected intravenously with quantities of dried copper-head venom diluted with saline solution and the results are incorporated in Table XIII. The sheep utilized weighed from 38·2 to 45·5 kilograms and the dosage administered varied between 0·002 and 0·04 milligramme per kilogram of body weight. No paralytic symptoms developed in animals receiving 0·02 to 0·05 milligramme per kilogram, but sheep No. 126 which had been injected with 0·075 milligramme per kilogram, developed an ataxic gait. Five out of seven animals injected with 0·1 to 0·4 milligramme per kilogram died from bulbar paralysis.

Sheep Nos. 165 and 122 which received 0·1 and 0·13 milligramme per kilogram respectively, recovered after periods of paralysis lasting one and five days. As in the case of the death adder, these results suggest that intravenous injections of copper-head venom may be less potent than similar amounts inoculated into the subcutaneous tissues, while calculations based on the available figures show a subcutaneous-intravenous index of 0·7.

The profundity and duration of the paralysis in sheep receiving sublethal doses of copper-head venom both on intravenous and subcutaneous injection were very striking and with no other venom do animals so profoundly paralysed recover. Clinical and *post mortem* observations on these animals showed that while hæmorrhagin, hæmolysin and anti-coagulin were present in the venom of *Denisonia superba*, thrombase was absent.

Experiments with Cobra Venom in Sheep.

Cobra (*Naia tripudians*) may be regarded as a standard colubride venom and for purposes of comparison with those of the Australian colubrides its subcutaneous and intravenous certainly lethal doses were determined in sheep and a few observations were also made on ligatured animals. The dried venom was supplied by the Haffkine Institute, Bombay, from supplies used in India for the production of cobra antivenene.

TABLE XIII.

The Intravenous Injections of Copper-head Venom (Denisonia superba) into Sheep.

Identification Number.	Weight in Kilograms.	Total Dosage in Milligrammes.	Dosage in Milligramme per Kilogram Body Weight.	Result.			Mode of Death.
				Recovered.	Paralytic Time.	Death Time.	
					Hours. Minutes.	Hours. Minutes.	
112	43·9	0·9	0·02	Yes	—	—	—
133	38·2	1·9	0·05	Yes	—	—	—
126	39·1	2·9	0·07	Yes; staggering gait	—	—	—
122	42·3	4·2	0·1	Yes	13 55	—	—
110	44·3	4·4	0·1	No	4 7	13 4	Neurotoxic
143	45·5	5·5	0·12	No	3 34	40 49	Neurotoxic
165	42·7	5·5	0·13	Yes	6 46	—	—
149	44·9	6·7	0·15	No	2 36	3 54	Neurotoxic
154	42·3	8·5	0·2	No	1 48	2 2	Neurotoxic
117	41·8	16·7	0·4	No	1 0	1 23	Neurotoxic

Animal No. 165 recovered after being completely paralysed for five days.
The strength of the venom varied from 2 to 10 milligrammes in 1 cubic centimetre.

TABLE XIV.

The Certainly Lethal Dose of Dried Cobra Venom (Naia tripudians) inoculated subcutaneously into Sheep.

Identification Number of Sheep.	Weight in Kilograms.	Total Dosage in Milligrammes.	Dosage in Milligramme per Kilogram Body Weight.	Result.		
				Recovered.	Paralytic Time.	Death Time.
					Hours. Minutes.	Hours. Minutes.
105	40·45	1·01	0·025	Yes	—	—
113	41·6	2·08	0·05	Yes	—	—
111	42·3	3·17	0·075	Yes	—	—
83	44·5	4·45	0·10	Yes	—	—
92	49·1	4·9	0·10	Yes	—	—
108	43·0	6·45	0·15	Yes	—	—
79	40·7	8·14	0·2	No	2 0	3 30
98	49·5	9·9	0·2	Yes; paralysed for 38 hours	6 45	Recovered
107	52·7	13·18	0·25	No	4 55	6 57
109	46·4	12·6	0·27	No	5 6	9 58
147	49·1	14·7	0·3	No	6 21	11 33
64	44·5	13·35	0·3	No	3 57	6 48
113	41·6	12·48	0·3	No	5 10	9 30
114	46·1	13·83	0·3	No	2 19	6 4
100	47·3	14·2	0·3	No	1 34	3 21
80	37·7	15·1	0·4	No	0 46	1 16
112	43·9	21·95	0·5	No	1 59	2 59

The venom was so diluted that 1 cubic centimetre contained from 5 to 20 milligrammes.
Animal No. 113 was inoculated five days previously with 2·08 milligrammes of cobra venom.

The Certainly Lethal Dose on Subcutaneous Injection.

Seventeen sheep varying in weight from 37·7 to 52·7 kilograms, were injected subcutaneously with doses of dried cobra venom appropriately diluted with saline solution varying from 0·025 to 0·5 milligramme per kilogram of body weight (see Table XIV). Six animals receiving less than 0·15 milligramme per kilogram recovered without becoming definitely paralysed. Of the two animals receiving 0·2 milligramme per kilogram, number 79 died in three and a half hours and number 98 survived, but only after having been completely paralysed for twenty-eight hours. The other nine sheep which received from 0·25 to 0·5 milligramme per kilogram, all succumbed, developing generalized paralysis and dying of bulbar paralysis and respiratory failure in the times indicated in Table XIV.

These observations show the subcutaneous certainly lethal dose to be 0·25 milligramme per kilogram, cobra venom being just one twenty-fifth as potent as tiger snake venom for ovines. It takes 12·5 milligrammes of cobra venom to kill a sheep of fifty kilograms (one hundred and ten pounds). Acton and Knowles[11] have estimated fifteen milligrammes to be the lethal dose for man and 0·25 milligramme per kilogram to be the certainly lethal dose for the rabbit. In terms of body weight, therefore, there appears to be little difference between the susceptibility of man, rabbit and sheep to cobra venom.

Ligature Experiments with Dried Venom.

The ineffectiveness of ligature in cobra bites, except as a measure for slightly prolonging the death time, is agreed upon by all observers and for this reason no extensive experiment was made on sheep. Two animals (numbers 146 and 164) weighing 46·8 and 45·5 kilograms respectively, were injected subcutaneously with 14·0 and 13·65 milligrammes of dried cobra venom in saline solution and a ligature was immediately applied for a period of thirty-five minutes. This dosage equalled 0·3 milligramme per kilogram of body weight and corresponded to one and a quarter certainly lethal doses of venom. The animals became paralysed in six hours and forty minutes and six hours and forty-eight minutes and died in ten hours and thirty-six minutes and fifteen hours and sixteen minutes respectively.

The control animal (number 147) which weighed 49·1 kilograms and received a corresponding dose of venom, that is 14·7 milligrammes or 0·3 milligramme per kilogram, became paralysed in six hours and twenty minutes and died in eleven hours and thirty-three minutes of respiratory failure. Actually the control animal became paralysed before the ligatured ones, while its death time was intermediate between them. Thus, as anticipated, ligature proved ineffective, but unfortunately not more so than for the various Australian colubrides under review.

TABLE XV.

The Intravenous Injection of Cobra Venom (Naia tripudians) in Sheep

Identification Number.	Weight in Kilograms.	Total Dosage in Milligrammes.	Dosage in Milligramme per Kilogram Body Weight.	Result.		
				Paralytic Time.	Death Time.	Mode of Death.
				Hours. Minutes.	Hours. Minutes.	
152	50·9	2·5	0·05	—	—	R.
153	49·1	4·9	0·10	—	—	R.
159	40·7	8·14	0·20	5 33	—	R.
156	48·2	12·05	0·25	1 0	2 39	Neurotoxic
155	50·5	15·15	0·30	1 0	1 55	Neurotoxic

The venom for animals Nos. 152 and 153 was diluted so that 1 cubic centimetre contained 5 milligrammes; in the other three 1 cubic centimetre contained 20 milligrammes.

R. indicates recovered.

The Certainly Lethal Dose on Intravenous Injection.

A series of observations on the end results of the intravenous injection of cobra venom in sheep will be found in Table XV. The usual procedure was followed and the dosage being varied from 0·05 to 0·3 milligramme per kilogram body weight. Animals Numbers 152 and 153 which received 0·05 and 0·1 milligramme per kilogram, made an uninterrupted recovery, but number 159, receiving 0·2 milligramme per kilogram, became paralysed for a period of three and a half hours and subsequently recovered. The others which received 0·25 and 0·3 milligramme per kilogram, died with neurotoxic features in two hours and thirty-nine minutes and one hour and thirty-five minutes respectively. Such results indicate that the intravenous and the subcutaneous certainly lethal dose approximate to one another and calculated on the basis of these figures, the subcutaneous-intravenous index would equal unity.

At autopsy evidences of the action of hæmorrhagin, hæmolysin and anticoagulin were obtained, but not of thrombase. In this respect as well as in regard to its neurotoxic action the similarity to death adder and copper-head venom was apparent.

The severity of the local lesions with this venom was very great and both sloughing of the tendons and gangrene of the soft tissues were noted. In some instances surgical amputation above the level of the metacarpo-phalangeal joint was indicated and in consequence several animals which had completely recovered from the systemic effects of the venom had to be destroyed.

The approximate certainly lethal dose of Russell's viper venom was taken as 1·25 milligrammes per kilogram, considerable variation in the susceptibility of different animals being observed.

Acton and Knowles[11] estimated the lethal dose for man as 42 milligrammes. The certainly lethal dose for a sheep of fifty kilograms (one hundred and ten pounds) is 62·5 milligrammes, so on this basis ovines appear to be less susceptible to Russell's viper venom than man.

Ligature Experiments with Dried Venom.

At the time these experiments were inaugurated I regarded the certainly lethal dose for sheep as being about one milligramme per kilogram. In consequence several of the animals received smaller quantities of venom than otherwise would have been the case. Nine animals were injected with from 51·8 to 61·4 milligrammes of dried venom, the dosage varying between 1·0 and 1·5 milligramme per kilogram of body weight (see Table XVII). Immediately afterwards the limb was ligatured for a continuous period of thirty-five minutes.

Of the four animals receiving one milligramme per kilogram only one recovered while another injected with 1·25 milligrammes per kilogram (one certainly lethal dose) survived. Four sheep were inoculated with 1·5 milligrammes per kilogram and of these two recovered. Thus three out of the five animals receiving 1·0 to 1·2 certainly lethal doses survived and it is only reasonable to attribute this life saving result to the effects of ligature. On the other hand three out of the four animals receiving less than the finally estimated lethal dose (1·25 milligrammes per kilogram) died despite ligature; its action is consequently subject to considerable individual irregularity. Even in the fatal cases,

TABLE XVI.

The Certainly Lethal Dose of Dried Russell's Viper Venom (Vipera russelli) for Sheep.

Identification Number of Sheep.	Weight in Kilograms.	Total Dosage in Milligrammes.	Dosage in Milligrammes per Kilogram Body Weight.	Result.		
				Recovered.	Collapse Time.	Death Time.
					Hours. Minutes.	Hours. Minutes.
111	42·3	10·6	0·25	Yes	—	—
83	44·5	22·25	0·50	Yes	—	—
108	43·0	32·25	0·75	No	1 41	1 54
140	47·3	36·9	0·78	Yes	—	—
92	49·1	49·1	1·00	No	—	Under 1 0
144	53·2	53·2	1·00	Yes	—	—
175	40·0	50·0	1·25	No	—	13 34
122	42·3	53·7	1·27	No	4 20	4 25
126	39·1	58·6	1·50	No	—	0 50
124	50·0	75·0	1·50	No	8 47	9 3
135	44·1	88·2	2·00	No	6 30	6 57

The venom was diluted so that 1 cubic centimetre contained from 10 to 50 milligrammes.
The cause of death in sheep No. 108 was portal thrombosis and in the case of Nos. 92 and 126 *ante mortem* thrombosis involved the pulmonary arteries and the right side of the heart as well as the portal system.

The Inoculation of Russell's Viper Venom in Sheep.

As these investigations progressed it appeared advisable to ascertain the susceptibility of sheep to a standard viperine venom and with this in view a series of these animals was inoculated with Russell's viper venom (*vipera russelli*) supplied to us by the Haffkine Institute, Bombay.

The Subcutaneous Certainly Lethal Dose.

Eleven sheep weighing between 39·1-53·2 kilograms were used and they received progressively increasing quantities of dried venom varying from 10·6 to 88·2 milligrammes. In terms of body weight the dosage was graduated from 0·25 to 2·0 milligrammes per kilogram (see Table XVI). Death did not occur with quantities of venom of less than 0·75 milligramme per kilogram and one animal survived 1·0 milligramme per kilogram. Sheep receiving 1·25 to 2·0 milligrammes invariably died, the cause of death being intravascular thrombosis, hæmorrhages or cardiac and vasomotor failure.

TABLE XVII.

Observations on the Effect of Ligature in Sheep subcutaneously inoculated with Russell's Viper Venom (Vipera russelli).

Identification Number.	Weight in Kilograms.	Total Venom in Milligrammes.	Dosage in Milligrammes per Kilogram Body Weight.	Result.		
				Collapse Time.	Death Time.	Mode of Death.
				Hours. Minutes.	Hours. Minutes.	
151	51·8	51·8	1·0	5 40	5 59	Portal thrombosis.
148	55·9	55·9	1·0	32 30	37 40	Cardiac failure and hæmorrhage.
141	53·2	53·2	1·0	—	—	—
161	53·2	53·2	1·0	24 55	28 15	Cardiac failure and hæmorrhage.
171	40·0	50·0	1·25	—	—	—
133	38·2	57·3	1·5	—	—	—
123	40·9	61·4	1·5	21 0	48 0	Cardiac failure and hæmorrhage.
176	40·0	60·0	1·5	13 50	13 58	Cardiac failure and hæmorrhage.
167	40·0	60·0	1·5	—	—	—

The venom was so diluted that 1 cubic centimetre contains 50 milligrammes of dried venom.
In animals Nos. 171, 176 and 167 ligature was applied for forty-five minutes and in the remainder for thirty-five minutes.

however, certain modifications of the clinical and pathological course resulted, for there was a definite prolongation of the death time when compared with control animals and death from *ante mortem* thrombosis involving the portal system only resulted once.

The Intravenous Certainly Lethal Dose.

Nine sheep were injected intravenously with Russell's viper venom receiving doses of from 0·025 to 0·50 milligramme per kilogram body weight. Two animals injected with 0·1 milligramme per kilogram succumbed, but one receiving 0·2 milligramme survived. Doses above this amount invariably proved fatal. The approximate certainly lethal dose on intravenous injection was taken as 0·25 milligramme per kilogram and as the subcutaneous certainly lethal dose is 1·25 milligrammes the subcutaneous-intravenous index equals 5. A perusal of Tables XVI and XVIII reveals, however, that the range of fatal dosage in individual animals varies more widely on intravenous (0·1 to 0·25 milligramme) than on subcutaneous injection (0·75 to 1·25 milligramme). It therefore follows that were it possible to make the estimation, the subcutaneous-intravenous index of certain individual animals would be of considerably higher value than 5.

THE SUBCUTANEOUS-INTRAVENOUS INDEX AND ITS SIGNIFICANCE.

The efficacy of ligature as a life-saving procedure in snake bite is very generally accepted as being related to the thrombase content of the inoculated venom and a perusal of experimental results obtained in rabbits with different venoms indicates this to be the case.

During experiments on sheep I was much impressed by the fact that, although my figures showed ovines to be five times more susceptible to subcutaneous inoculations of tiger snake venom than Tidswell[8] had found rabbits to be, yet on intravenous injection sheep succumbed to approximately the same dosage of venom as rabbits when this was expressed as milligrammes per kilogram of body weight.[1] Evidently different species of animals may show wide variations in their susceptibilities not only to venom as a whole, but also to its different constituents.

TABLE XVIII.

The Intravenous Injection of Russell's Viper Venom (Vipera russelli) into Sheep.

Identification Number.	Weight in Kilograms.	Total Dosage in Milligrammes.	Dosage in Milligramme per Kilogram Body Weight	Result.		
				Collapse Time.	Death Time.	Cause of Death.
				Hours. Minutes.	Hours. Minutes.	
136	47·5	1·19	0·025	—	—	R.
137	46·4	2·32	0·05	—	—	R.
138	46·4	4·64	0·10	0 16	0 19	Intracardiac and portal thrombosis.
142	42·0	4·2	0·10	0 42	0 48	Intracardiac and portal thrombosis.
150	44·8	8·96	0·20	—	—	R.
139	50·9	12·73	0·25	21 21	21 46	Gastric hæmorrhage.
158	44·5	11·25	0·25	2 31	2 36	Vasomotor and heart failure.
163	52·3	15·7	0·30	4 32	4 42	Vasomotor and heart failure.
145	50·9	25·45	0·50	. 7	0 47	Portal thrombosis.

The venom was so diluted that 1 cubic centimetre contained from 10 to 50 milligrammes.
R. indicates recovered.

[1] The actual venom utilized in these sheep experiments has recently been titrated in rabbits by Kellaway at this Institute. The subcutaneous certainly lethal dose was found to be 0·045 milligramme per kilogram and the intravenous certainly lethal dose to equal 0·002 milligramme per kilogram.

Thus sheep proved only two-fifths as susceptible to thrombase as rabbits per kilogram of body weight and 4·5 times more sensitive to the neurotoxic constituents of the tiger snake venom actually used in the present investigation.

In the present series of experiments ligature in both sheep and goats had proved ineffective, whereas Martin had conclusively demonstrated is efficacy on rabbits subcutaneously injected with six certainly lethal doses. Questions naturally arose as to whether the diverse lethal effects exerted by tiger snake venom in these two species of animals on subcutaneous and intravenous injection depended on their variable susceptibility to neurotoxin on the one hand and thrombase on the other and also whether this relationship might not underlie the divergent results observed in ligature experiments on rabbits and sheep respectively.

The three killing constituents in venoms are neurotoxin, hæmorrhagin and thrombase, the first of these being the cause of deaths in all colubride bites and the last two being chiefly concerned in the case of the vipers.

In all the Australian colubrides hæmorrhagin is poorly represented and it may be dismissed as a lethal factor in these venoms. Thrombase on the other hand is present in large quantities in *Notechis scutatus* and *Pseudechis porphyriacus*.

The lethal effects of thrombase are dependent on its concentration in the circulation and unless very large doses are injected subcutaneously, it does not give rise to intravascular thrombosis and death. Small doses introduced intravenously are, however, very lethal and this is the route of election for the demonstration of the thrombase content of any venom especially where hæmorrhagin is absent or only present in small amounts.

On the other hand, the lethal effect of neurotoxin is generally about the same whether it be introduced into the subcutaneous tissues or directly into the venous system, except that the death time is often shortened by the latter procedure.

It appears therefore that in the absence of considerable quantities of hæmorrhagin in a given venom, subcutaneous injection will afford an index to its neurotoxic and intravenous injection to its thrombase constituents and that in consequence the subcutaneous-intravenous index can be employed to ascertain the relative susceptibilities of a given species of animal to these two substances.

With this object in mind the subcutaneous-intravenous index, which is obtained by dividing the subcutaneous by the intravenous certainly lethal dose, was ascertained in sheep and goats for the various venoms under investigation and in addition relevant data bearing on the subject were collected from the literature and analysed from this point of view.

The rabbit is the only animal in which both routes of injection have been at all frequently practised, and it also happens to have been the laboratory animal most widely utilized in ligature experiments by previous observers. In a limited number of instances, therefore, it has been possible to determine whether the subcutaneous-intravenous index would have afforded information regarding the probable efficacy or inefficiency of ligature in rabbits inoculated with a range of colubride and viperide venoms.

Ligature in Rabbits.

Martin and McGarvie Smith[12] in a paper dealing with black snake venom pointed out that the intravenous or subcutaneous method of introduction made a difference of at least a decimal point in the lethal dose; they also found that 0·01 grain injected intravenously would constantly kill a five pound rabbit in about one hundred seconds, that is a dose of 0·0286 milligramme per kilogram.

Tidswell[8] reported the minimum lethal dose on subcutaneous injection to be 0·6 milligramme per kilogram and on this basis the subcutaneous-intravenous index would be 21. The same observer found the subcutaneous minimum lethal dose of tiger snake venom to be 0·5 milligramme per kilogram and the intravenous minimum lethal dose to equal 0·004 milligramme per kilogram. This would give a subcutaneous-intravenous index of 12·25, but calculated on the basis of Kellaway's more recent figures a value of 22·5 is obtained. For *Echis carinata* Martin and Lamb[3] report the subcutaneous certainly lethal dose as one to two milligrammes and the intravenous certainly lethal dose as 0·05 milligramme, the subcutaneous-intravenous index being 20.

In the case of the Daboia (*Vipera russelli*) Acton and Knowles[11] found the subminimal lethal dose on subcutaneous injection to vary between three and ten milligrammes and on intravenous injection to equal 0·27 milligramme. Calculated on this basis the subcutaneous-intravenous index would be 11 to 37.

The figures of the same observers for the cobra (*Naia tripudians*) show a subcutaneous-intravenous index of 2·3, while Lamb's results[13] in the case of the common krait (*Bungarus cæruleus*) and the banded krait (*Bungarus fasciatus*) show it to be 2·0 and 3·6 respectively.

It is interesting to note that all of these venoms showing a high subcutaneous-intravenous index also possess the property of producing intravascular clotting when injected into the blood stream. This is evident in the case of viperine snakes, *Echis carinata* and *Vipera russelli*, but it is also a feature of the Australian colubrides, *Pseudechis porphyriacus* and *Notechis scutatus*, whose venoms were shown by Martin to be rich in thrombase. In the case of the banded krait the subcutaneous-intravenous index was 3·6 and this is of special interest as Lamb[13] found its poison to possess the property of inducing intravascular clotting *in vivo*, whereas no definite results were obtained with citrate plasma *in vitro*. Thrombase is absent from the venom of the cobra and the common krait.

In this series of observations a high subcutaneous-intravenous index obtains only with venoms containing thrombase. Further in the Australian venoms if this thermolabile constituent is removed by heating to an appropriate temperature, leaving its neurotoxin intact, the intravenous approximates to the subcutaneous lethal dose and as shown by Martin[2] ligature becomes ineffective even for rabbits.

When the efficacy of ligature is considered we find that good results have been reported following experimental inoculation of rabbits in the case of tiger snake, black snake and Russell's viper. Experimental results are not available for *Echis carinata,* but clinical evidence indicates its therapeutic value. It should be noted that in every instance the subcutaneous-intravenous index for these venoms exceeds 10.

In the case of the cobra and both krait venoms on the other hand the subcutaneous-intravenous index was invariably low, never exceeding 3·6, and both experimental and clinical evidence show that ligature merely prolonged the death time. Thus ligature proved efficient only when the subcutaneous-intravenous index was high. In the next section the results of the present series of experiments on sheep and goats are analysed from that point of view.

Ligature in Sheep and Goats.

The end results of the various ligature experiments are epitomized in Table XIX, a perusal of which shows that complete failure occurred with four of the venoms investigated, and that in all instances the subcutaneous-intravenous index was low (0·8 to 2·0), whereas it was sometimes effective with Russell's viper venom in which the subcutaneous-intravenous index was somewhat higher (5·0).

Colubride Venom Containing no Thrombase.

The typical colubride venoms kill by neurotoxin and contain no thrombase and copper-head and death adder venoms resemble cobra venom in this respect. In consequence nothing more than a prolongation of the death time could be anticipated from the application of ligature. This was fully borne out by the experimental results which showed definitely that in each instance ligature failed to save life even when only one to two certainly lethal doses of venom were inoculated. The subcutaneous-intravenous index in all these venoms was invariably low, never exceeding unity. With cobra it equalled 1·0 and in the case of the death adder and copper-head 0·9 and 0·7 respectively, intravenous injection proving less lethal than subcutaneous injections with the last two venoms. It is known that on subcutaneous injection neurotoxin immediately begins to enter the circulation and continues doing so until the process of absorption is completed. When the intravenous route is employed, there is a sudden high concentration of venom in the circulating blood instead of a gradually increasing concentration over a longer period. The kidneys definitely possess some power of excreting venom and under these conditions it is probable that a fraction of the circulating neurotoxin is eliminated by renal secretion or otherwise secreted or destroyed before its localization in the ganglion cells of the central nervous system has been completed. During the present study the presence of neurotoxin in the urine was not investigated, but the data available certainly indicate that the mechanism for dealing with sudden concentrations of copper-head and death adder venom in the circulation is well developed in ovines and that this is the explanation of the low subcutaneous-intravenous indices obtained.

Colubride Venoms Containing Thrombase.

Tiger snake venom contains much thrombase and Houssay and Negrette[14] actually place it first of all the coagulant venoms in order of positive activity. It also contains large amounts of a most lethal neurotoxin, but hæmorrhagin is poorly represented.

Determinations of the subcutaneous-intravenous index showed it to be 2·0 in the case of sheep, 4·5 in goats and 22·5 in rabbits, while ligature has been found effective only in the latter animals. All these species readily succumb to whole venom on subcutaneous injection, but their relative degrees of susceptibility to venom injected intravenously were subject to considerable variations.

Even after circulatory stasis has been induced by ligature, the mere presence of thrombase in the inoculated venom is not necessarily sufficient to lock up its neurotoxin and other constituents effectively *in situ* and contrary to Martin's results in rabbits *post mortem* evidence of increased local coagulation and thrombosis in the vicinity of the inoculations was no more definite in ligatured sheep and goats than in non-ligatured animals. Another factor is evidently essential. This is a high degree of reactivity on the part of the blood and tissue fluids of the inoculated animal to thrombase, so that very small doses relative to the other venom constituents will produce clotting.

In the case of the Australian colubride venoms this information is afforded by the subcutaneous-intravenous index and it is only in animals like the rabbit in which high indices are obtained (22·5), that ligature is found to be effective. In those species such as sheep and goats, which are highly susceptible to neurotoxin and relatively less so to throm-

TABLE XIX.

The Subcutaneous-intravenous Index in Sheep and Its Essential Relationship to the Efficacy of Ligature.

Species of Snake.	Certainly Lethal Dose in Milligrammes per Kilogram of Body Weight.		The Subcutaneous-intravenous Index.	Result of Ligature.
	Subcutaneous Injection.	Intravenous Injection.		
Tiger snake	0·01	0·005	2·0	Failure
Death adder	0·025	0·0275	0·9	Failure
Copper-head	0·1	0·15	0·7	Failure
Cobra	0·25	0·25	1·0	Failure
Russell's viper	1·25	0·25	5·0	Sometimes effective

base, lower readings are found (2·0 to 4·5) and ligature is ineffective.

Finally, attention is directed to the fact that the rabbit which has been so widely utilized in experiments on ligature, is probably unsuitable for this purpose owing to its abnormal sensitiveness to thrombase relative to neurotoxin. This is clearly shown by the very high subcutaneous-intravenous indices obtained in this animal with all the thrombase-containing venoms (20·0 to 37·0) compared with the lower indices found with the same venoms in other species. Attention has been already directed to the low indices obtained with tiger snake venom in sheep (2·0) and goats (4·5), while Kellaway's recent figures for other laboratory animals were likewise low, being 2·9 for the guinea-pig and 6·0 for both the mouse and the rat.

The main thesis of the present paper is that before the results of ligature experiments with any given venom can be transferred to man, it is necessary to establish its efficacy over a series of animals showing low as well as high subcutaneous-intravenous indices.

The sheep is relatively insusceptible to thrombase, yet even here under conditions of natural bite rapid death from portal or pulmonary thrombosis and *ante mortem* clotting in the right side of the heart may sometimes be observed. In man, however, these findings have never been recorded. At autopsy the blood always shows the negative phase of decreased coagulability or an entire failure to clot, while death invariably results from neurotoxic paralysis of the bulbar and other centres. These facts suggest that man is highly susceptible to the neurotoxin constituent of tiger snake venom without being unduly sensitive to thrombase, a state of affairs which in sheep has been shown to underlie the ineffectiveness of ligature.

Viperine Venoms.

The killing constituents in viperine venoms are hæmorrhagin and thrombase, neurotoxin being poorly represented as a rule. Considerable amounts of the first two substances are generally present, but some, notably *Crotalus adamanteus*, are anticoagulant in action. Noguchi[5] found that in rabbits the subcutaneous and the intravenous certainly lethal dose was 0·005 milligramme and 0·0002 milligramme respectively, the subcutaneous-intravenous index being 25. This venom contains large quantities of hæmorrhagin, but no thrombase and its enhanced action on intravenous injection is due to destructive lytic effects exerted on the endothelial lining of the vessels of important internal organs rather than on those of the subcutaneous tissues. It follows that in viperine venoms a high subcutaneous-intravenous index does not necessarily mean that ligature will be effective, though it is necessarily ineffective in any venom which produces low subcutaneous-intravenous indices.

In ligature experiments on sheep inoculated with Russell's viper venom, three out of five animals receiving 1·0 to 1·2 certainly lethal doses, recovered, whereas others receiving less than the estimated certainly lethal dose died despite ligature. Its action was very uncertain and similarly in experiments conducted by Acton and Knowles several ligatured rabbits succumbed to doses of venom from which others recovered. Varying individual susceptibility to thrombase probably accounts for these anomalies. Support for this view is found in the data of Table XVIII in which the lethal dose on intravenous injection of sheep was found to vary from 0·1 to 0·25 milligramme per kilogram.

Summary and Conclusions.

1. The absorption time of a lethal dose of tiger snake venom in sheep naturally bitten was estimated as not exceeding two minutes.

2. The subcutaneous and the intravenous certainly lethal doses of tiger snake, copper-head, death adder, cobra and Russell's viper venoms were determined for sheep.

3. Thrombase was shown to be absent from both death adder and copper-head venoms and in experiments on sheep ligature did nothing more than prolong the death time.

4. In experimental inoculation of ovines with the tiger snake venom which contains thrombase, both intermittent and continous ligature proved equally ineffective.

5. In goats inoculated subcutaneously with tiger snake venom continuous ligature also failed to save life even when only one certainly lethal dose was injected.

6. In the case of colubride snakes the quotient of the subcutaneous certainly lethal dose divided by the intravenous certainly lethal dose was found to afford important information regarding the value of ligature. The term subcutaneous-intravenous index has been introduced to designate this ratio.

7. In colubride venom high indices (ten to thirty) are found when ligature is successful, but with viperine venom, owing to its high hæmorrhagin content, a high index may occur when ligature fails.

8. Ligature is never successful in the presence of a low subcutaneous-intravenous index (0·7 to 2·5).

9. Before the results of animal experiments can be transferred to man the efficacy of ligature must be established in a series of animals. Rabbits are unsuitable for this purpose owing to their high sensitivity to thrombase.

10. When these criteria are adopted, the present experimental findings do not support the therapeutic value of ligature in the Australian colubrides, except as a measure of permitting other modes of treatment and prolonging the death time.

Acknowledgements.

We are greatly indebted to Professor Woodruff and Mr. Albiston of the Veterinary Research Institute for providing accommodation for the large series of animals used in these experiments. Accommodation at the Walter and Eliza Hall Institute is inadequate for such a purpose and without the cooperation of the Veterinary School, work on this scale could not have been undertaken. Colonel F. P.

Mackie, O.B.E., I.M.S., Director of the Haffkine Institute, Bombay, generously supplied us with the cobra and Russell's viper venom used throughout the experiments.

REFERENCES.

(1) S. Weir Mitchell: "Researches Upon the Venom of the Rattlesnake," *Smithsonian Contribution to Knowledge* (Pub. Smithsonian Institution, Washington), 1860, Volume XII, page 109.
(1a) S. Weir Mitchell: "On the Treatment of Rattlesnake Bites with Experimental Criticisms upon the Various Remedies Now in Use," *North American Medical and Chirurgical Review*, 1861, Volume V, page 269.
(2) C. J. Martin: T. C. Allbutt's "System of Medicine," 1897, Volume II, page 828.
(3) C. J. Martin and G. Lamb: Allbutt and Rolleston's "System of Medicine," 1907, Volume II, Part II, page 783.
(4) H. W. Acton and R. Knowles: "Studies in the Treatment of Snake Bite," *Indian Journal of Medical Research*, 1914, Volume II, page 91.
(5) H. Noguchi: "Snake Venoms," *Carnegie Institution of Washington*, 1909, Chapter XXX, page 287; also page 72.
(6) V. Brazil: "*La défense contre l'ophidisme*," S. Paulo, 1914, page 229.
(7) M. L. Crimmins: "Texas Snakes and their Poisons," *Journal of the Veterinary Medical Association*, 1927, Volume XXIV, page 704.
(8) F. Tidswell: "Researches on Australian Venoms," Sydney, 1906, page 16.
(9) C. J. Martin: "On the Physiological Action of the Venom of the Australian Black Snake (*Pseudechis porphyriacus*)," *Journal of the Royal Society of New South Wales*, 1895, Volume XXIX, page 146.
(10) A. MacInnes: "Treatment of Snake Bite," THE MEDICAL JOURNAL OF AUSTRALIA, May 21, 1927, page 771.
(11) H. W. Acton and R. Knowles: W. Byam and R. G. Archibald's "The Practice of Medicine in the Tropics," 1921, Volume I, Section V, page 683.
(12) C. J. Martin and J. McGarvie Smith: "The Venom of the Australian Black Snake," *Proceedings of the Royal Society of New South Wales*, 1892, Volume XXVI, page 240.
(13) G. Lamb: "Some Observations on the Poison of the Banded Krait (*Bungarus fasciatus*)," *Scientific Memoirs of the Government of India No.* 7, 1904, page 17.
(14) B. A. Houssay and J. Negrette: *VII Influencia de los venenos de serpientes sobre la coagulacion de la sangre Kev. Inst. Bacteriol. Buenos Aires*, 1918, Volume I, No. 5, page 565.

Reviews.

DIABETES MELLITUS.

IN an inspiring preface Dr. Elliott P. Joslin introduces to the medical profession the fourth edition of his "Treatment of Diabetes Mellitus" and we feel bound to state that the book justifies his optimism.[1]

Dr. Joslin writes: "Diabetes and especially diabetic children are here to stay. Years ago I longed to buy them an island or a continent where they could grow up without realizing what they missed, but they would resent such an habitat to-day, because modern medicine has made them superior to their disease."

The introduction of "Insulin" has been responsible for this changed attitude towards and the outlook for the diabetic and Joslin in the section on "Insulin" gives a very full account of its action and use, of the difficulties that may occur in its use and of the methods of overcoming those difficulties. He is especially insistent on the value of "Insulin" in the treatment of children and we can fully endorse all his optimism. His frontispiece portrait of a healthy looking young woman of twenty years who has just celebrated her tenth diabetic birthday, should convince the most sceptical. Joslin insists that when using "Insulin" diabetics must still be carefully dieted, but points out that though the diet must be properly balanced in regard to the ration of carbohydrates, protein and fat, it can and should be made adequate in caloric value to the patient's working requirements and that then the patient should lead his normal life, whether it be at school, at play or at business or other work. This is perhaps the greatest change that has occurred in the attitude towards the diabetic patient since the publication of the previous edition.

Joslin has tried the use of "Synthalin," "Myrtalin" and other proposed substitutes for "Insulin" with generally disappointing results and in many cases with harmful effect and it is evident that we have as yet no substitute for "Insulin" in our treatment.

There is a full discussion of all the other problems of diabetes with many case quotations which make very interesting reading. The chapter on coma and its treatment should be read and reread by every medical practitioner, for this complication is apt to appear with dramatic suddenness and unexpectedness; there is no excuse for inefficient treatment in the presence of such a chapter as Joslin presents.

Five years ago the treatment of diabetes was almost a nightmare. Today it is a joy and a delight to anyone who will take the trouble to master such a book as Dr. Joslin has presented to us, and we would commend it to the general practitioners of Australasia as a book that they cannot afford to be without. Further, if they will but start its perusal, they will find it so fascinating that there is little fear they will not read its pages to the end.

[1] "The Treatment of Diabetes Mellitus," by Elliott P. Joslin, M.D. (Harvard), M.A. (Yale); Fourth Edition, Enlarged, Revised and Rewritten; 1928. Philadelphia: Lea and Febiger; Sydney: Angus and Robertson, Limited. Royal 8vo., pp. 998, with illustrations. Price: 45s. net.

CARDIO-VASCULAR PRESSURE.

THE variations of pressure in the different chambers of the heart and at different regions of the vascular system are an important dynamic factor in maintaining the circulation. In "The Pressure Pulses in the Cardio-Vascular System," by C. J. Wiggers, the investigation of pressures has been undertaken and the results detailed.[1] Hitherto there has been considerable diversity in the records obtained by different observers; this has been due chiefly to instrumental causes, a lack of sensitivity being the main reason. Sir Thomas Lewis remarks that the history of pressure curves is the history of instruments. Optical manometers which have a high "figure of merit," have been used by the author in his experiments. Certain criteria of efficiency have been postulated for recording instruments and these have been adopted in taking the records. As a result of this and the evident care which has been taken to insure accuracy, and the clearness with which they are presented, the observations should do much to clarify the position as regards pressure curves.

The writer states that the study of the pressure pulses not only acquaints us with the pressure values at different parts of the circulation, but supplies information as to velocity and volume of the blood flow which depend on the differences of pressure in the different regions. The nature of fractionate contraction in the auricles and ventricles, the dynamic function of the auricle and the part the latter plays in ventricular filling, the importance of the contraction of the interventricular septum, are discussed from the point of view of their effects on pressure. A new light is thus thrown on the sequence of dynamic events in the auricles and ventricles. The form of the arterial pulse and the pressure relations during abnormal cardiac mechanisms are described and are of especial interest. After reading the book one is impressed with the importance of "pressure" in the circulatory system.

[1] "The Pressure Pulses in the Cardiovascular System," by Carl J. Wiggers, M.D.; 1926. London: Longmans, Green & Co. Ltd. Demy 8vo., pp. 212.

The Medical Journal of Australia

SATURDAY, MARCH 23, 1929.

The Embley Memorial.

On May 9, 1924, a great Australian sank into his last long sleep. Edward Henry Embley during the course of many years contributed toward the establishment of a high reputation of Australian scientists. Few men have possessed the spirit of inquiry to a greater degree and few have trained themselves more adequately for research work. The world is indebted to Edward Henry Embley for having revealed the physiology of chloroform poisoning. It is true that others have investigated the toxic action of drugs and have established beyond question how some of the poisonous substances can be employed in therapeutics with safety. The work of a sound pharmacologist is always valuable, but it is rarely epoch-making. The inestimable benefit to mankind of anæsthesia threatened to become almost a danger toward the end of last century when chloroform was administered on a plan based on the false doctrines of the physiology of the drug. Some anæsthetists were able to induce chloroform anæsthesia with scarcely any risk. But they were not numerous. Accidents became common and many were fatal. Efforts were made to replace chloroform by ether, but these were not at first entirely successful. During the last decade of last century ether was administered with the aid of the Clover or similar apparatus and the disadvantages of these closed methods soon became apparent. Pulmonary congestion manifested itself in the majority of patients; vomiting was the rule and post-anæsthetic pneumonia was all too common. In the 'nineties ether was reserved for healthy adults up to middle age; chloroform was held to be safer for children and old people and for patients with cardiac lesions or myocardial defects, with debilitating affections and with renal disease. Some sound work had been conducted in Glasgow some time previously, on which the pharmacological action of chloroform vapour was based. Waller continued and extended this work and carried our knowledge some steps further. Then the celebrated Hyderabad Commission was appointed and its findings threatened to destroy all the scientific investigations that had been accomplished up to that time. Edward Henry Embley recognized the importance of the problem to humanity and as a true scientist he set himself the task of discovering the truth. Never before nor since has the futility of casuistic observation as opposed to planned physiological research been more strikingly demonstrated. Many practitioners of medicine scoff at work conducted in the laboratory and prefer to rely on clinical impressions and arm-chair hypotheses or even superstitions that have found their way into text books generations ago and have remain unchallenged as orthodox doctrines. Embley accepted the challenge of the clinicians and with the collaboration of Professor (now Sir) Charles J. Martin he proved to the world how foolish it was to start at the wrong end of a difficult problem. He proved each step in his investigations and he laid bare the complete record of his evidence. Those who had understanding, recognized that his findings must form the lasting basis for a proper understanding of the action of choloroform intoxication. It is not suggested that he disclosed the whole story. Vision, patience, keenness of intellect, honesty and punctillious care in regard to small details gained a signal victory over rash guess work and in this way Embley again vindicated the authority of the laboratory. His other researches were conducted with same spirit of inquiry, of determination to wrest the truth from the obscuring folds of Nature's mantle, of basing conclusions on facts. The example he has set to those who have come and will yet come after him, must not be lost. The Council of the Victorian Branch of the British Medical Association has been wise in its determination to erect a permanent memorial to Edward Henry Embley and his great work. The form of the memorial will depend on the magnitude of the response to the invitation to subscribe to the fund. Those who knew Edward Henry Embley will scarcely need persuasion; they will delight in con-

tributing to a memorial to their revered friend. There must be many who know of Embley's work, but who have been deprived of the advantage of a personal acquaintance. They will realize that the memorial will stand for all that is highest in scientific research, the quest for truth without thought of personal gain. As Embley gave to the world and to his own profession the fruits of his large intellect and the products of his untiring labours, so his colleagues who have derived benefit from the knowledge obtained from this invaluable work, will wish to give freely. Donations should be sent to Dr. C. H. Mollison, the Honorary Treasurer of the Victorian Branch, 41, Collins Street, Melbourne, C. 1, as early as possible and not later than April 15, 1929. We hope to publish the list of donations to the memorial fund of a great Australian.

Current Comment.

THE PHYSIOLOGY OF THE THYREOID.

Since the publication of the important work on the physiology of the thyreoid gland by G. S. Williamson and I. H. Pearse in 1925 and 1926 the conception of its normal and abnormal manifestations has undergone considerable alteration. The classification of the several types of goître has been placed on a more satisfactory basis and hyperthyreoidism has been invested with a new significance. It will be remembered that Williamson and Pearse have shown that the functional activity of the thyreoid is twofold. There is a colloid-storing phase and a secretory phase. An account of these views will be found in The Medical Journal of Australia of April 3 and 10, 1926. In a recent communication[1] these authors state that the conception is gaining ground that these two events are best studied as two distinct functions. They produce most interesting evidence in support of this view, drawn from a study of the results of therapy in Graves's disease. Their report is concerned only with material taken from patients treated in two different ways: by partial removal of the gland when iodine treatment was carefully excluded and by partial removal of the gland when preoperative treatment was consistently used. There were 403 patients in the former or "non-iodized" group and 104 in the latter or "iodized" group. The patients included none but those with the full clinical syndrome of Graves's disease. The one feature common to all thyreoid glands in Graves's disease is their "secretory" activity. Abundant iodo-colloid may be present, but it may have disappeared, leaving a non-colloid goître. Graves's disease is the only non-colloid goître disease. For this reason it is called adenoid goître. The secretion from an adenoid goître contains no iodine.

The observations of Williamson and Pearse are concerned with the effect of treatment on the iodo-colloid function of the gland. In the non-iodized group 193 adenoid goîtres occurred in the 403 patients, an incidence of 48%. The tissue removed in these 193 glands contained no colloid and the secretion within the follicles contained no iodine. There were 33 out of the 403 patients untreated with iodine whose treatment proceeded in two or three stages. Of the specimens removed at the first operation 28 yielded material which contained no colloid. Although some iodine was present in seven of the 23 specimens tested by the tadpole test, the iodine was inactive and had not the effect of thyroxin. A striking change was found in all the material removed from the twenty-eight patients at the second operation. Every specimen contained iodo-colloid tissue as well as "secretion" tissue. The amount of each tissue varied within the widest limits. Both types had all the characters of tissue found in the normal glands. No iodine had been administered in the interim. It is inferred that the iodine necessary for this change was in the body at the time of the first operation and that as a result of the operation it was released and made available for storage. Further, an excess of secreting tissue operates as an inhibitory factor, preventing the storage of iodo-colloid in the thyreoid. Reference will be made to this later.

The results noted in the "iodized" group are equally interesting. Among the 104 specimens received after operation there were only two adenoid goîtres. When this is compared with the figure of 48% noted in the non-iodized group, it must be owned that Williamson and Pearse are justified in their statement that iodine treatment practically abolishes adenoid goîtres from the goîtres of Graves's disease. The findings of the effect of iodine on the secreting tissue and on the iodo-colloid tissue were the same as those of all other workers. Both secreting tissue and iodo-colloid tissue were present. The quantity of iodo-colloid stored bore no relationship to the amount of iodine ingested. In two instances, in spite of intensive feeding with iodine, no iodo-colloid appeared. Moreover, it was not apparent that iodine feeding reduced the actual amount of active secreting tissue. After investigation it was determined that the secretion in the secreting tissue retained its normal character in spite of the iodine treatment and that the colloid which appeared, conformed to what is known of normal colloid. The effect of the iodine treatment is summarized as the provision in a primarily non-colloid gland of a store of normal iodo-colloid; the iodine did not inhibit secretory activity, nor did it affect permanently the symptoms of the disease.

The natural outcome of this work is the discussion by Williamson and Pearse of the various

[1] *The Quarterly Journal of Medicine*, October, 1928.

theories which have been put forward to explain Graves's disease, toxic goître and endemic goître. They point out that each theory is based on the supposition that secretion proper and iodo-colloid are mutually derivative substances. They proceed by the logical application of their observations to show that this is not so. Secretion is not the mother substance of iodo-colloid, otherwise accumulation of iodo-colloid would be accompanied by secretory activity. Again, if the secretory activity were dependent upon an excessive demand for circulating iodine, the secretory activity would be evident in the well-filled iodo-colloid follicles, but it is not. Secretion contains no iodine and the modicum of iodine present in secretory tissue is inactive. If secretory activity were dependent on an excessive demand for circulating iodine, the demand could not be satisfied by diminishing the supply, as is done by operation in Graves's disease. Iodo-colloid also can be stored at the same time as secretory activity is maintained. According to the dystrophy theory of the iodo-colloid function in Graves's disease, secretion is said to be thyroxin-poor colloid; in other words the secretion is the residue after iodo-colloid has been deprived of its iodine molecule. In these circumstances iodo-colloid would be the mother substance of secretion; the theory would explain secretory activity by presuming a disorganization of the iodo-colloid function of the thyreoid in Graves's disease. But the iodo-colloid function of the thyreoid is not disorganized; this is proved by the fact that removal of part of the gland is followed by storage of iodo-colloid in the remaining part of the gland. In some way secreting tissue is apparently responsible for keeping the iodo-colloid mobilized. Williamson and Pearse insist that it is the opportunity rather than the capability to elaborate iodo-colloid that is lacking in the gland in Graves's disease. They also go on to show that there is no evidence to show that iodo-colloid is the mother substance of secretion.

After claiming to have justified the view that there are two separate functions in the thyreoid gland, Williamson and Pearse go on to state that the intoxication of the thyreoid gland should be spoken of as associated with a disturbance of the secretory function of the thyreoid gland. They claim that this disturbance is not a quantitative one, but hold that there is evidence that there is for each gland a critical amount of secretory activity which iodine treatment cannot displace. "This critical amount may occupy the whole goître and so prohibit iodo-colloid storage."

It will be admitted that these observers have made out a good case for the existence of two functions of the gland. The existence of two functions in other organs is not unknown. The pancreas, for example, has its acinar cells and its islet cells. An American observer has isolated two hormones from the posterior part of the pituitary gland. The arguments which have been summarized above, point to the correctness of the claim that iodo-colloid and secretion do not stand to either in the relationship of either cause or effect. It would have been interesting, however, if they had allowed themselves to speculate further as to the relationship to one another of the two functions which they describe. That there is a relationship between the functions is most likely. Evidence has been offered that the presence of a disorder of secretion prevents storage of iodo-colloid. This must be a gradual process; otherwise there would be a much larger percentage of adenoid goîtres than forty-eight among those persons with Graves's disease who have not been treated with iodine. It would appear that secretion, apart from the possibility of having a direct function of its own, may have a regulating influence as far as the storage of iodo-colloid is concerned. In health, when sufficient iodo-colloid has been stored for the needs of the body, secretion steps in and acts either directly or in a reflex way on the cells producing iodo-colloid and its production is suspended. If there were a disorder of secretion, as Williamson and Pearse suggest, secretion would accumulate and the already stored-up iodo-colloid would be used up gradually to supply the body needs. When it had all been dissipated, the condition described as adenoma (non-colloid goître) would be present. It would be difficult to explain the action of iodine therapy, unless it were held that the excess of secretion either locked up the iodine present in other parts of the body or locked it out of the thyreoid cells. Still more difficult would it be to find an explanation of the effect of operation in allowing storage of iodo-colloid to be resumed. What really remains to be determined is what are the conditions which initiate a secretory phase and what those which bring about an iodo-colloid phase in a normal gland.

SIGNED ARTICLES IN THE LAY PRESS.

On March 14 there appeared in the general cable news of one of the great daily newspapers of Australia an announcement that the General Medical Council has approved the issue of a series of signed articles under the auspices of the Society of Medical Officers of Health and that the first article is on influenza by a member of that society. Our contemporary comments on the change of policy on the part of the General Medical Council. It is stated that this body has hitherto been strongly opposed to signed articles by medical men in the public press. Although its findings are not yet available, it is obvious to every one who has knowledge of the rulings of this statutory body that its warning to medical practitioners on this subject has not been amended or modified. The warning is addressed to members of the profession who are engaged in private practice. Whole-time medical officers of the public services are not included and the General Medical Council would certainly regard announcements by bodies like the Society of Medical Officers of Health or their nominees as being in the public interest.

Abstracts from Current Medical Literature.

MORBID ANATOMY.

Chronic Ulcer of the Œsophagus.

M. J. STEWART AND S. J. HARTFALL (*The Journal of Pathology and Bacteriology*, January, 1929) report a case of chronic peptic ulcer of the lower end of the œsophagus. The ulcer measured fifty by forty-four millimetres and was situated immediately above the gastro-œsophageal junction. The chief symptoms were pain, situated high in the epigastrium, of five months' duration and hæmatemesis for a fortnight. Dysphagia was not a prominent symptom. Death was due to perforation of the ulcer into the right pleural sac. The œsophagus above the ulcer was slightly hypertrophied and dilated and in its upper part just below the level of the cricoid cartilage there were two symmetrically disposed areas of heterotopic gastric mucosa, each twenty-five millimetres in length and five and seven millimetres in breadth respectively. These consisted of fundal type of mucous membrane with abundant oxyntic cells and the authors have no doubt that they were capable of secreting acid gastric juice. They point out that gastric heterotopia in the upper part of the œsophagus is by no means rare, but that the misplaced islets of mucous membrane are usually small. Ordinarily the secretion from these glands must be rapidly diluted and neutralized by saliva and carried onwards into the stomach. If acute peptic ulceration of the œsophagus should occur in a person with extensive gastric heterotopia, the spasm of the cardia which is liable to be set up, may lead to the accumulation of considerable quantities of acid secretion above the closed orifice. This in turn may play a part in delaying the healing of the ulcer.

The Preparation of Pen and Ink Drawings of Specimens.

T. SHENNAN (*The Journal of Pathology and Bacteriology*, January, 1929) gives details of a method of preparing drawings of pathological specimens. An ordinary black and white photographic print is made, preferably on a matt surface paper. On this print the outlines and details are drawn with a fine drawing pen, a good waterproof Indian ink being used. It is necessary to wipe the point of the pen repeatedly during this process on a piece of old linen. The irregularities and varying shades can be reproduced fairly well by the stipple method. A certain amount of shading can be produced by drawing closely set parallel lines in the parts which are in shadow. A fine camel hair brush is used for blocking out. The print is then discharged. The print is treated with 1% watery solution of iodine until the paper is of a deep blue-black colour. It is then rinsed in water and treated with hyposulphite solution containing citric acid. The formula is as follows: 5% acid "hypo," 600 cubic centimetres; citric acid, 7·5 grammes with 30 cubic centimetres of hot water; sodium sulphite, 15 grammes with 30 cubic centimetres of hot water. The solutions of citric acid and sodium sulphite are mixed and then added to the 5% "hypo" solution. The paper is then washed for an hour in running water and allowed to dry. The resulting drawing may be touched up if necessary with the pen point.

Phagocytosis of Vascular Endothelium.

F. A. MCJUNKIN (*The American Journal of Pathology*, November, 1928) has investigated the phagocytic activity of the vascular endothelium of granulation tissue. He has produced areas of granulation tissue in rats and has subsequently introduced India ink into the circulation. The carbon granules were found in the vascular endothelial cells. When the injections were given subcutaneously, carbon was also found in the endothelial cells, but not to the same extent. The presence of carbon in the cells can be explained only by phagocytosis. In view of these findings the author considers that the blood vascular endothelium must be considered as a possible source of mononuclear phagocytes.

Pulmonary Pigmentations and Anthracosis.

ANDRÉ JOUSSET (*La Presse Médicale*, April 14, 1928) as a result of chemical and histological investigations, maintains that so-called anthracosis is in nearly all cases a siderosis, the result of some previous inflammatory process in the lung. The chemical tests of earlier investigators were, he holds, inadequate and did not prove that the pigment found in the lungs of old people was carbon. If the colour were due to inhaling smoke, it would appear greatest in the hilar regions, as it is in coal miners who have true anthracosis. In the aged it is very patchy in its distribution. Pulmonary pigmentation is found in still-born infants and in those who have lived only in the country. On the other hand the lungs of old city dwellers have been found at autopsy to be quite free from pigment. Finally, this patchy type cannot be produced experimentally. All the evidence shows that the pigment is not air-borne, but is due to some pathological process. Jousset claims that by careful chemical and metallurgical tests which he describes, he has proved that the constant black pigment found in lungs is an albuminous compound of iron and is not carbon at all. He then discusses the origin of this pigment. The so-called "dust cells," he believes, play no heroic part in protecting the lung tissues from damage or destruction, as do the polymorphonuclear cells. They are merely scavengers of waste pigment; "melanocytes" he terms them. They are identical in significance with the "cardiac cells" of chronic pulmonary congestion of cardiac origin. Both contain pigment, the result of hæmolysis, in the one due to chronic congestion, in the other due to chronic inflammation. The pulmonary pigmentation, then, is always pathological and not a normal process. This explains the clear lungs of certain aged city dwellers; they have escaped any pulmonary inflammations. Instead of a physiological anthracosis there is a pathological siderosis. To the objection that these pigmented lungs may be normal in all other respects, the author replies that the slightest congestion will suffice and few during life escape this entirely. He maintains that there is, of course, scarring as well and in proportion to the pigmentation, though it is not so readily observed. Tuberculosis affords an excellent example of the truth of his contention. It is not that it occurs in a lung damaged by anthracosis, but that the disease sets up the reaction of siderosis. On this hypothesis the origin of collections of pigment in the midst of scar tissue, far from the air passages and hitherto baffling to pathologists, is now quite obvious. According to this conception Jousset believes that all the organs and especially the lungs, can, under inflammatory stress, acquire that normal function of the liver, a capacity of mobilizing the waste iron pigments.

MORPHOLOGY.

The Breeding Season of the Opossum.

CARL G. HARTMANN (*Journal of Morphology and Physiology*, September 5, 1928) states that the breeding season of the opossum (*Didelphis virginiana*) at Austin, Texas, begins in January, following a three months anœstrus or resting period during October, November and December. There is a slight variation in the breeding season from year to year. Ovulation reaches a maximum during the third week of January. In the southern States there are at least two litters a year, with some evidence of a third, probably produced by unusually fecund females. The rate of intrauterine development was investigated chiefly by surgical removal of one uterus, the stage of the contained ova for a precalculated period being noted. Biometrical methods were employed as far as possible and the results of the investigation illustrated in unique charts. The gestation period of approximately thirteen days is subject to great variations as in other mammals; the first half of gestation concerns the differentiation of the "proembryo" and at seven and a half days *post coitum* (seven days *post ovulationem*) the primitive streak is completed and the formation of the medullary plate and notochord begun, while the actual intrauterine development of the embryo comprises the

remaining five and a half days. The embryonic growth curve for the period concerned coincides with that of higher mammals and man. The average litter weight to the body weight of the mother is in the ratio of one to a thousand. The eyes and mouth may open at fifty days *post partum* or may even remain closed for a longer period. The young are weaned at about eighty days, soon after which the mother may again become pregnant, although the first litter may not become independent until ninety to a hundred days after birth.

Carbon Dioxide Tension and Cell Division.

J. C. Mottram (*The British Journal of Experimental Pathology*, October, 1928) has made observations on the effect of carbon dioxide atmospheres of varying pressures on cultures of normal cells and sarcoma cells *in vitro*. Normal mitoses were most abundant at a carbon dioxide tension which approximated to that of normal living tissues, that is of forty millimetres, while abnormal mitosis occurred at high tensions. It was also observed that the size of the nuclei of undividing cells under high tension was increased and reduced under low tension, as compared with normal cells at forty millimetres pressures. These observations are of interest from the point of view of the somatic mutation theory first suggested by Boveri (1914) that by unequal chromatin division somatic mutations might arise which would give to cells abnormal characters. The production of mutations by radiation is now an established fact, but as high carbon dioxide tension may also cause abnormal mitoses, the somatic mutation hypothesis appears to cover a wider field other than that of radiation. The influence of carbon dioxide suggests that somatic mutations might be caused in tissues by an interference of the blood supply.

Fibroblasts of Jensen Sarcoma.

A. Carrel and A. H. Ebling (*Journal of Experimental Medicine*, Volume XLVIII, 1928) state that although the fibroblasts obtained from a fragment of Jensen sarcoma differ from rat fibroblasts observed in pure cultures, by the refringement aspects of the cytoplasm and its coarseness they appear to be morphologically true fibroblasts. These cells, when cultivated *in vitro* as a pure strain for several months, retain their malignancy and give rise to tumours on inoculation. The tumours thus produced are transplantable and kill animals without producing any metastases. The importance of pure strain *in vitro* cultures is emphasized when a comparison is made with the older hanging drop methods of fifteen years ago. Abnormalities and degenerative phenomena are common in the latter, whereas the pure strain fibroblasts cultivated with modern technique are quite uniform in morphological characters; there are no abnormal mitoses and few binucleate cells can be seen. Normal fibroblasts do not proliferate in blood serum, whereas the Jensen fibroblasts multiply rapidly in that medium. Such a difference in the food requirements of Jensen and normal fibroblasts is probably due to increased acid production and proteolytic power of the tumour cell.

The Nervous System of the Opossum.

O. Langworthy (*Journal of Comparative Neurology*, August 15, 1928) outlines the result of his investigations into the myelinization of the cord and brain stem of pouch-young opossums, at the same time correlating these observations with the periods at which various reflexes are present. The observations were limited to animals more than four weeks old, owing to the technical difficulties of the study of myelinization in earlier stages. The studies involved were of considerable importance in connexion with the general belief that as various functions appear, these are associated with the appearance of myelinization in the brain stem and cord. So far as his evidence went, Langworthy believed that these studies supported this hypothesis. Further interesting facts were observed, for instance the efferent side of a reflex arc is medullated before the afferent side; again, it was observed that when cerebellar connexions became myelinated, the movements of the animal became less ataxic, more steady and better coordinated. The postural reflex developes at the time when the rubrospinal pathway is acquiring its myelin component. Again, when medullated fibres may be seen on the optic nerve and followed to the superior colliculus of the midbrain, the opossum's eyes open. In general the fibres in the central nervous system become myelinated in the order in which they have developed phylogenetically. The evidence that tracts in the central nervous system become medullated at the time when they become functional, is, however, by no means positive. It is impossible to escape the fact that this animal is also capable of complicated reflex activity before any myelinated fibres are present.

The Resistant Ectoderm of the Negro.

S. J. Holmes (*American Journal of Physical Anthropology*, July-September, 1928) outlines his studies upon the immunity of the American negro, more especially to skin diseases, such as erysipelas *et cetera*. Again, infections of the nose are less prevalent, while eye defects were observed less frequently among negro recruits for the Great War. As regards cancer, cancer of the skin is relatively rarer among negroes than among whites, while the relations are reversed in, for example, cancer of the uterus. Among epidemic diseases the negroes enjoy a definite immunity to scarlet fever, diphtheria and to a less degree measles. That the cause of the negro's low morbidity and mortality rates from diphtheria is local instead of constitutional is indicated by the fact that the proportion of Schick reactions is about the same among negroes and whites and by the fact that when negroes once contract diphtheria, the mortality rate is high. The immunities of the negro may be plausibly interpreted from one common standpoint as a result of the greater resistance of the ectodermic layer of the skin and the invaginated linings of the buccal and nasal cavities. Resistance to diphtheria, scarlet fever and measles may result from the same peculiarities which render the negro relatively free from diseases of the skin. Differences in the susceptibility of races to diseases may depend upon variations in local reactions of the parts in which invading germs make their first real inroads as contrasted with mere mechanical lodgment.

Relationship of the Dental Follicle and Dental Roots to the Maxillary Sinus.

H. Runge (*Zeitschrift für Anatomie und Entwicklungsgeschichte*, May, 1928) gives a survey of the exact relationships at different ages of the dental follicles of the various teeth, both deciduous and permanent, to the antrum of Highmore. He made use of eighteen heads of children of all ages from those newly born to nineteen years of age. In some instances X ray pictures were used. Many of the preparations were from specimens decalcified by Killian's method and hardened in formalin. After a careful description of each head, combined with diagrams in each case, the author summarizes his results. The milk follicle and later the erupted milk canine tooth is never closer than 5·5 millimetres to the maxillary sinus. The milk molar follicles gradually come closer and closer to the floor of the sinus as it enlarges, so that they are ultimately only 2·0 to 1·5 millimetres from it. On eruption the tooth roots of these milk molars again become separated for a considerable distance from the sinus and this distance increases with age exactly as with milk canine teeth. As regards the permanent teeth, the permanent canine follicle and the root of the erupted tooth lie in close proximity to the sinus up till the fifteenth year, from this age onwards the distance from the sinus steadily increases except in unusual instances. Its exact relationship varies, the tooth sometimes lying more in relationship to the floor and sometimes more in relationship to the anterior wall of the sinus. The roots of the first premolar tooth approach the sinus very closely from sixteen years onwards, while the follicle also approaches the sinus very closely. As would be expected, the second premolar is still closer. Finally the first and second permanent molars have both their follicles and roots in close relationship to the floor of the sinus at all ages, without exception. The author reviews the literature and publishes an extensive bibliography.

British Medical Association News.

SCIENTIFIC.

A meeting of the Northern Division of the Tasmanian Branch of the British Medical Association was held on October 27 and 29, 1928. A series of post-graduate lectures and demonstrations was given at the Launceston Public Hospital by Mr. R. M. Downes, Honorary Surgeon to the Children's Hospital, Melbourne, and Mr. R. Fowler, Honorary Gynæcologist to the Alfred Hospital, Melbourne.

Heliotherapy.

Mr. Downes gave a lecture on heliotherapy. He said that although they were apt to think that the utilization of the power of the sun in the treatment and prevention of disease was a very recent development, it was as a matter of fact one of the most ancient curative methods recorded in history.

There was evidence that nearly five hundred years B.C. Hippocrates was aware of the physical and curative action of the sun and references to its use by the ancient Greeks and Romans were frequent. From their time to the eighteenth century it appeared that little use had been made of it as a curative agent, but in the last century more and more recognition had been given to its value, its present position being due chiefly to the incentive given by the happy results obtained by Bernhard and Rollier in the treatment of wounds and tuberculosis in alpine climates since the beginning of the present century and repeated by Gauvain in England. The recent brilliant discoveries of the mechanism of sunlight in the prevention and cure of rickets had produced something like a "boom" in England. The pioneer of this method in Victoria, and Mr. Downes believed in Australia, was Kent Hughes who had introduced it some five years previously at the Melbourne Children's Hospital in the treatment of surgical tuberculosis.

It was in regard to surgical tuberculosis that he would attempt to place the more important practical features of heliotherapy before them, but a few remarks on its theoretical aspect were necessary.

The rays emitted by the sun consisted of heat or infra-red rays, visible rays or light and invisible chemical or ultra-violet rays; these rays, however, occupied a very minute part of the whole spectrum of radiant energy as at present known. If the visible spectrum were represented as one foot in length, the whole spectrum would occupy some millions of miles. The various constituents of the spectrum were distinguished by their wave lengths, in other words, by the distance between successive waves; at one end were the Hertzian waves, some of which were used in wireless telegraphy, whose wave lengths reach several kilometres; at the other were the γ rays of radium, with a wave length of 0·01 Ångström units. The Ångström unit, the most commonly used unit of measurement, represented one ten-millionth part of a millimetre. Even shorter waves had been discovered.

Though the heat and visible rays of the sun had curative properties, it was the ultra-violet rays that appeared to be of the greatest value. The ultra-violet rays were readily absorbed by many elements. First of all the atmosphere absorbed them, particularly the short ultra-violet rays, so that considerably less penetrated to sea level than reached high mountains. The severity of sunburn so quickly sustained on mountains, especially when the mountains were covered with snow which reflected 70% to 80% of the ultra-violet rays, was an everyday illustration of this. Since in early morning and evening the sun's rays had to traverse a greater distance through the envelope of the earths' atmosphere than at midday when the sun was overhead, it followed that more ultra-violet rays reached the earth's surface at midday. Fog and dust still more so absorbed them readily and for this reason little was present in the sunlight reaching large cities.

In addition to the direct rays of the sun a great deal of diffused ultra-violet rays came from the sky. When the sun was highest, the ultra-violet rays from the blue sky were 15% more than from the direct sun. From a cloudy sky even ultra-violet rays were obtained, though of much less intensity. The practical application was that they could carry out heliotherapy in the shade or even on cloudy days, though a proportionately longer time was required for the same effect.

Returning to the solar spectrum, Mr. Downes said that the visible rays seen when light was broken up into its constituent parts by the familiar spectrum extended from 4,000 Ångström units at the violet end to 8,000 Ångström units at the red end. For the detection of ultra-violet rays a photographic plate was used or a screen coated with a solution that became fluorescent under their influence. The beam which contained them was first passed through a quartz lamp prism which passed rays of as low a wave length as 1,850 Ångström units and broke them up in the same way as the glass prism of the ordinary spectroscope. The shortest waves arising from the sun were 2,900 Ångström units under the best circumstances. Those considered most active biologically lay just below 3,000 Ångström units. Ordinary window glass transmitted practically none below 3,300 Ångström units. It was apparent, therefore, that glass-covered solaria were inefficient. There was a special glass known at "Vitaglass" which, acting similarly to quartz, allowed most of the ultra-violet rays of sunlight to pass and could be used instead of ordinary window pane glass when the benefits of heliotherapy were wanted, as in schools, hospitals or animal houses.

The effects of heliotherapy on the human being were numerous and the great amount of research that was being carried out on the subject, was daily adding to the knowledge of them, though many of their physiological and pathological effects were still far from clear.

Mr. Downes went on to speak chiefly of those that are observed in the everyday application of heliotherapy. He said that first of all there was the great improvement in what, to use a military term, they might call morâle. It was really remarkable in a heliotherapy ward and most gratifying to hear the noise from and see the obvious happiness of these children, all bedridden and in splints of some kind or other, many with discharging sinuses and lying there month after month under strict discipline. Then the improvement in their general appearance was astonishing; with the deep pigmentation which must be regarded as the essential feature in the picture, there was a rounding off of curves, a pliability of skin and increase of development until many of the children gained the appearance of the absolute fitness of the trained athlete or habitual surf bather. In some children the increase in weight and stature was considerable and rapid.

Regarding pigmentation it was generally held, particularly by Rollier, that prognosis could be based largely on the production of pigmentation and that in those who browned well, the prognosis was good and *vice versa*. How pigmentation acted was not clear. Pigment consisting of melanin granules deposited in the deep cells of the epidermis as a result of the action of the ultra-violet rays, definitely transformed ultra-violet rays into heat and was a protection against the lethal action of too large a dose. In addition there were two theories associating the beneficial effect of ultra-violet rays with the phenomenon of pigmentation. According to one, the pigment transformed in the tissues light rays into some other form of radiation which had a beneficial effect. The other postulated the production of substances which got into the circulation in unrecognizable form and acted curatively on tuberculous foci. Whatever the truth of either of these theories, it appeared to be a fact that improvement in condition marched with the intensity of pigmentation.

Another prominent feature was the resistance to cold acquired by children under treatment. Lying naked all day, except for a small cotton "V" over the pubes, the only covering they required at night up to the end of May was a cotton sheet and at no time in the winter did they have more than one blanket and a half. And it took only a few weeks to accustom a newcomer to these conditions.

There was evidence also that mental development was increased under light therapy, for Gauvain had found

that the average mental age of insolated children was greater than that of the untreated child.

Among several effects of the application of heliotherapy, as shown by laboratory investigations, the great rise in metabolism which was manifested by an increase in respiratory activity and appetite, might be mentioned. This, however, was due in part to the stimulating effect of the fresh air on the bare skin which was a necessary adjunct to the sun's rays, and no less an essential in the treatment of surgical tuberculosis.

Among local effects, decrease of pain in inflamed joints and superficial inflammations were noticeable, while the skin surface was sterilized by the destruction of bacteria. It should be mentioned, too, that the penetration of the skin by ultra-violet rays was of the slightest; only the longer rays penetrated at all and then only through one-tenth of a millimetre of skin.

In considering the method of use of this form of treatment it should be remembered that it was not foolproof. The personal experiences of undue sunburn which all had undergone, would illustrate that. A great deal of harm could be caused by over-sunning and caution should be used at the beginning of the treatment, particularly in mountain climates; at the sea level the danger was not so great. As a guide the following plan might be used for sea level in summer.

On the first day the legs and feet should be exposed for ten minutes; on the second the thighs for ten and the legs for twenty minutes; on the third the abdomen for ten, the thighs for twenty and the legs for thirty minutes; on the fourth the chest for ten minutes and so on in accordance with the accompanying table. The head should always be kept covered with a white hat.

Region.	Day of Treatment.										
	1	2	3	4	5	6	7	8	9	10	11
	Mins.	Mins.	Mins.	Mins.	Mins.	Mins.	Mins.	Mins.	Mins.	Mins.	Mins.
Legs and feet ..	10	20	30	40	50	60	90	120	120	120	120
Thighs ..	—	10	20	30	40	50	60	90	120	120	120
Abdomen	—	—	10	20	30	40	50	60	90	120	120
Chest ..	—	—	—	10	20	30	40	50	60	90	120

If the patient could be turned over, similar exposures should be given to the dorsal aspect as to the ventral. After the patient had become used to a two hours' exposure, he could continue in the sun as long as he felt no discomfort from it.

For winter the initial times might be doubled and the two hours' exposure reached in eight days. Some patients were much more sensitive to sunshine than others and the times given might require lessening. The one criterion of overdosage was discomfort in any form. If the child began to cry or object, if he seemed seedy or lost his appetite after sunning, had a rise of temperature over 37·8° C. (100° F.) or became badly burned, he had had too much. At any time if children asked to be taken in out of the sun, this should be done. The early morning was the best time for treatment, for though the intensity of the ultra-violet rays was not so great as towards midday, the heat was avoided which later in the day might become too great. For this reason heliotherapy wards in the southern hemisphere sould be built facing the north-east. Some degree of warmth was, however, desirable, for the effect of the ultra-violet rays was greater in the presence of warmth and their effects were lessened by cold. In cold weather patients should be screened from the wind, for notwithstanding their acquired resistance to cold, children could stand very little cold wind on their bodies, even in bright sunshine.

In regard to tuberculosis which offered the greatest field for this treatment it was a general action that was aimed at rather than local. Though ulceration of the skin around the cloaca of a sinus might improve under local radiation, the greater the area of skin exposed to the sun, the greater the general improvement to be expected. Under the treatment the discharge from sinuses was generally increased at first, but became more serous and in favourable cases might cease entirely. The actual skin should be exposed; it hardly needed to be mentioned that any clothes absorbed the ultra-violet rays before they could reach the skin. If for any reason clothes had to be worn, artificial silk or open meshed white cotton garments were the most suitable. Any grease applied to the skin interfered with the action of the rays; hence the common practice of applying vaseline to the skin to prevent sunburn. In carrying out sun treatment not only should caution be observed generally in preventing burning and harmful toxic effects to the patient, but there were some special indications for care. The more fair in complexion a patient was, the more likely he was to become burned and the less likely to become pigmented. Red haired and freckled children were particularly unfavourable subjects; they became but little pigmented and were easily made ill by too much exposure. In them, as in all individuals, it was the skin normally little exposed to the sun that had to be treated with most care. When fever was present, direct sunshine should be abandoned. In pulmonary tuberculosis the treatment, if given at all, should be carried out with the greatest care or harm would result. Renal disease was another contraindication.

As well as in skeletal and glandular tuberculosis, which was at present its greatest field, heliotherapy was valuable in other diseases. Rickets, although little in evidence in Australia, was entirely prevented and cured by sunshine as by administration of cod liver oil; in each case this was due to the action of the antirhachitic vitamin *D*, present in cod liver oil and formed from ergosterol, normally present in the body by the action of ultra-violet rays of wave length between 2,900 and 3,200 Ångström units. In infantile paralysis great help might be derived from sunshine as far as regaining power in muscles partially paralysed was concerned.

There was a large field, too, in the treatment of ulcers, lacerations and burns. Freely discharging and painful œdematous wounds or ulcers were quickly improved, pain ceasing, the surface drying and surrounding epithelium spreading inwards. In a children's hospital this could be applied with great hopes to children with osteo-myelitis after operation, where the relief of pain associated with changing of dressings was worth a great deal; but most strikingly in cases of burns. Not only did they do away with the misery of daily dressings and the profuse discharge so common, but the truly astounding rapidity with which even large raw areas become covered with epithelium, difficult and not always successful grafting operations thus being saved, made sunshine the most valuable single method they had in this most distresssing condition.

In relation to heliotherapy the artificial production of ultra-violet rays by lamps of various designs had to be considered. There were some who claimed superiority for the artificial method, regarding it as analagous to the synthetic form of a crude drug. While avoiding entering into any technical argument as to the superiority of one method over the other, it was clear that it was advisable to reinforce sun treatment by the artificial source. If they had sunshine every day it might not be so, but in the Australian climate there were many days on which they had little or none at all, and on these days the lamps were required. There were several types of lamps, the most convenient for general use being the mercury vapour lamp. In this the mercury enclosed in a quartz tube was vapourized by an electric current giving off a wide range of ultra-violet, visible and heat rays. There were two types of burner; one from which the air was exhausted to create a partial vacuum could be used with alternating or direct current; the other, more powerful and cheaper, the atmosphere type, was suitable only for direct current. They were inexpensive to operate and had a long life.

There were numerous conditions for which they might be used with advantage, particularly skin diseases, for which sunshine could not be very well employed. The dosage could be adjusted more accurately by varying the time of exposure and distance from the lamp than in the case of sunshine. The artificial ultra-violet ray treatment perhaps suffered in reputation from the multiplicity of

diseases it was said to cure, but its value was undoubted as an adjunct to heliotherapy in surgical tuberculosis.

The Fallopian Tubes.

MR. R. FOWLER gave a lecture demonstration entitled "Occlusive Salpingopathy." He illustrated his remarks by a practical demonstration of transuterine gas inflation.

Tuberculous Lesions in Children.

MR. DOWNES gave a lecture demonstration on common tuberculous lesions in children, osteomyelitis and rare lesions of bones. He showed numerous pathological specimens and X ray photographs.

Prolapse of the Female Genitalia.

MR. FOWLER gave a lecture on "Prolapse of the Female Genitalia." He professed his adherence to the Manchester School (Dr. W. E. Fothergill). He said that it was necessary to recognize as genital prolapse four conditions and three combinations of these conditions. Enumerated these were: (i) Cystocele, (ii) classical prolapse of uterus (in three degrees of severity), (iii) elongate loose uterus inverting vagina from above downwards, (iv) rectocele, (v) cystocele with rectocele, (vi) *prolapsus uteri* with rectocele, (vii) long loose uterus with rectocele.

The clinical characteristics of each type were discussed together with appropriate operations for their relief. Mr. Fowler held that the wisdom of Fothergill's insistence upon the futility of abdominal operations and the success of vagino-plastic procedures he advocated were borne out in practice.

The lecture was illustrated by lantern slides and the lecturer answered numerous questions.

Mr. Fowler also gave a practical demonstration of "Lipiodol" salpingoskiagraphy. An X ray photograph was taken and demonstrated by the lecturer.

MEDAL OF THE ASSOCIATION IN AUSTRALIA.

ON February 9, 1922, the Federal Committee of the British Medical Association in Australia resolved on the motion of Dr. W. N. Robertson, C.B.E., on behalf of the Queensland Branch, that the Federal Committee institute a gold medal to be bestowed from time to time upon members of the British Medical Association who have rendered signal service to the medical profession.

A year later the Federal Committee resolved to bestow the gold medal on Dr. R. H. Todd and Dr. W. T. Hayward. On November 12, 1923, Sir George Syme as President of the first session of the Australasian Medical Congress (British Medical Association), Melbourne, made the presentation of the two medals during the inaugural meeting of Congress. A short account of Sir George Syme's remarks, together with illustrations of the gold medal, were published in THE MEDICAL JOURNAL OF AUSTRALIA, December 22, 1923.

On March 5, 1929, a special meeting was held in the B.M.A. Building, 30 to 34, Elizabeth Street, Sydney, for the purpose of the presentation of the gold medal of the Branches of the British Medical Association in Australia to Dr. W. H. Crago. The formal presentation will be made at the inaugural meeting of the third session of the Australasian Medical Congress (British Medical Association) on September 2, 1929. An informal presentation took place on March 5, when Sir George Syme, Chairman of the Federal Committee, and many other Fellows of the College of Surgeons of Australasia were in Sydney for the annual meeting of the College.

Sir George Syme in presenting the medal to Dr. W. H. Crago, pointed out that the award was for signal service to the profession. Dr. Crago had been a member of the British Medical Association since 1884, a period of forty-five years. He had been elected a member of the Council of the New South Wales Branch in 1889 and had held the position of Honorary Treasurer from 1889 to 1893, when he became Vice-President. In 1894 he occupied the chair as President of the Branch. In 1895 he again became Treasurer, which position he had retained for thirty-eight years up to the date of the meeting. He commented on this long and sterling service he had given to the Branch. *The Australasian Medical Gazette* had been purchased from the late Ludwig Bruck by the New South Wales Branch in the year during Dr. Crago had been President. Dr. Crago had undertaken the management of this publication from 1895 until 1914, when *The Australasian Medical Gazette* together with its contemporary *The Australian Medical Journal* had ceased to appear. Dr. Crago had been the Chairman of Directors of the Australasian Medical Publishing Company, Limited, from its inception in 1913 until 1924.

In 1909 at the instance of Dr. Crago and of Dr. G. H. Abbott, while the latter was President of the New South Wales Branch, it had been decided to purchase the site of 30 to 34, Elizabeth Street, Sydney, and to erect the B.M.A. Building on that site. Dr. Crago has acted as premises' attorney ever since. Dr. Crago has been selected to be the Honorary Treasurer of the ninth session of the Australasian Medical Congress in 1911 and he had again been selected to fill the same position in the third session of the new congress which would be held in September, 1929, in Sydney.

When the Federal Committee established the Medical Officers' Relief Fund in 1919 for the assistance of dependants of those members who had fallen on active service and of those who had returned with physical or mental injuries from the war, Dr. Crago, together with Dr. George Armstrong and Dr. R. Gordon Craig, had accepted the positions of trustees. Dr. Crago had acted as Secretary of the Fund since 1919. In addition Dr. Crago had carried out the work of Honorary Auditor to the Federal Committee since its establishment in 1912. Dr. Crago had been the honorary Treasurer of the New South Medical Union for fifteen years from 1914 to 1919.

Sir George Syme concluded with some references to Dr. Crago's personal qualities and reminded his audience that in his professional capacity as a surgeon Dr. Crago could boast that he was the only one who had a patient alive thirty years after he had removed a hydatid cyst from the brain.

In the course of a short reply, Dr. Crago said that he wished to correct an impression Sir George Syme had left. It was Dr. Abbott who should be given the credit for the determination to build the building in Elizabeth Street. He (Dr. Crago) had advocated the erection of premises for the Branch, but Dr. Abbott had translated the general desire into a practical scheme during his tenure of the office of President. He thanked Sir George Syme.

NOMINATIONS AND ELECTIONS.

THE undermentioned have been nominated for election as members of the New South Wales Branch of the British Medical Association:

Delamothe, Peter Roylance, M.B., 1928 (Univ. Sydney), 50, Milton Street, Ashfield.

Thomson, George Macdonald, M.B., B.S., 1928 (Univ. Sydney), Sydney Hospital, Sydney.

THE undermentioned has been elected a member of the Victorian Branch of the British Medical Association:

Bastow, John, M.B., B.S., 1928 (Univ. Melbourne), Alfred Hospital, Prahran.

Special Correspondence.

CANADA LETTER.

BY OUR SPECIAL CORRESPONDENT.

Medicine in Canada.

WHAT is in the womb of the future for medicine? The probability of an epidemic of "flu" visiting Canada called

for in military parlance a mobilization of state medicine to fight the invader. Health bulletins are eagerly scanned to see how the tide of war is going. State medicine, judging from its bulletins, is far more optimistic than the rank and file at grips with the enemy in the front trenches. The propaganda in the bulletins—call your doctor, pure air, wholesome food, sleep, recreation, sunshine *et alia*—seems to be getting from the man on the street about the par evalution of the antics of the "bulls and bears" of Wall Street. Will state medicine through its bulletins receive the same attention in the near future now given to those of the weather bureau, stock market or society columns? Will people daily scan the medical bulletin to see what they must do in order to avoid disease and to keep well?

The year 1928 was a very progressive one in Canadian medicine. The first five months were very busy ones in the medical departments of our universities and in the hospitals associated with them. The paramount production of our medical departments is the general practitioner. Our young graduates can all join Sir Berkeley Moynihan in saying: "I am a physician, practising medicine, surgery, gynæcology." One lamentable void in the medical curriculum is the absence of any adequate instruction in physiotherapy. Were the writer a young graduate again, he would not feel justified in attempting to practise without an efficient training in the science and in the art of physiotherapy. June in medicine as in matrimony is a very busy month in Canada. The graduates receive their degrees, medical associations hold their annual meetings and the brides rush to the hymeneal altars.

Annual Meeting.

The picturesque city of Charlottetown on the Atlantic seaboard attracted physicians from all over the Dominion, some from the United States and from Europe to the annual meeting of the Canadian Medical Association held there in June. The best traditions in the science and in the art of medicine were well maintained in the papers presented by representative men.

The aphorism, "time does not kill," was verified when in October the medical profession of Nova Scotia assembled *en masse* at Halifax to attend the seventy-eighth annual meeting of the Nova Scotia Medical Society. The papers and discussions displayed normal vitality and reflected the best in the traditions, literature and practice of medicine.

The medical profession of New Brunswick was highly honoured and one of the sublimest traditions in medicine, unselfish service, inculcated when the Minister of Health, the Honourable Dr. Taylor, asked for leave of absence in order to attend patients in a sparsely settled district who could not obtain medical attendance.

Quebec, though overwhelming French, is steadfast in her loyalty to both the British Commonwealth and to the Dominion of Canada. Her chief city, Montreal, is the metropolis of Canada. It was here in Magill University that Sir William Osler half a century ago laid the foundation on which he built his international reputation. The annual meeting of the Canadian Medical Association will be held here in June.

A mammoth home is being erected just north of the Toronto General Hospital for the devotees of research work, pathology, physiology and kindred subjects. It will be connected by a tunnel under College Street with the hospital.

The Late Clarence Starr.

Our profession sustained a grievous loss recently in the premature death of Dr. Clarence Starr, chief of the surgical departments of the university and hospital. He died in middle life, but had already attained an international reputation.

Antituberculosis Work.

The Sun Life Assurance Company of Canada initiated a most beneficent innovation when it placed thirty scholarships at the disposal of the Canadian Tuberculosis Association. Thirty-two representative medical members of this association, accompanied by wife or relative, in all seventy persons, sailed from Montreal on August 24, 1928, to make a careful survey of antituberculosis work in Great Britain, France, Italy and Switzerland. The problems investigated included municipal housing schemes, sanatorium construction and equipment, diagnostic and therapeutic measures, post-sanatorium care and the like. These specialists brought back a very valuable fund of knowledge which it is hoped may be very efficiently diffused.

The British Medical Association Meeting of 1930.

Medical eyes all over the civilized world and may we hope especially in Australia will be turning towards Winnipeg, where the British Medical Association meets in the summer of 1930. Winnipeg is the metropolis of the many cities and towns scattered over the illimitable space, four thousand miles to the Yukon and north to the polar regions, like Australia in extent. Our western people have a world-wide reputation for hospitality, so that those coming from Australia and all over the world will find a most cordial welcome to the hearts and homes of the Canadian people. The two great transcontinental railway systems, Canadian National and Canadian Pacific Railways, will doubtless arrange for many delightful excursions at reduced rates. These great systems are unexcelled for comfort, safety, speed and courtesy. They have a magnificent chain of palatial hotels extending from coast to coast, where every want is provided for. The scenery from Atlantic to Pacific, about four thousand miles, is varied and charming and through the Rocky mountains thrilling and spectacular beyond all conception.

Correspondence.

SEPTUM OF THE UTERUS.

SIR: The following case exhibits a feature of such unusual interest that we feel it worth recording.

Mrs. V., *ætatis* thirty-eight years, had thrice previously miscarried, once at three months, a second time at six weeks and the third at three months, each time without obvious cause and with a negative Wassermann.

Most anxious to have a living child she was again pregnant and without incident up to the fourth month when to her chagrin she awoke one night to find herself in a pool of amniotic fluid, the inevitable miscarriage following two days later. The fœtus was spontaneously expelled, but the decidua remaining, manual removal was performed.

Whilst exploring the uterus we were surprised to find a definite ring of fibromuscular tissue extending from the midline of the fundus down into the cavity of the uterus for about one and a half inches in an antero-posterior direction.

Apparently a crude attempt at the formation of a double uterus had been made and we had encountered an incomplete perforate septum, the mechanism of which in producing abortion would be obvious.

Yours, etc.,
H. W. LORDING, B.A., M.B., B.S.

Obituary.

BERNARD JAMES NEWMARCH.

WE regret to announce the death of Dr. Bernard James Newmarch which occurred at Sydney on March 15, 1929.

CUTHBERT ARNOLD VERGE.

IT is with regret that we announce the death of Dr. Cuthbert Arnold Verge which occurred at Sydney on March 15, 1929.

Books Received.

THE HUMAN BODY, by Marie Carmichael Stopes; 1929. London: G. P. Putman's Sons. Demy 8vo., pp. 224, with illustrations. Price: 3s. 6d. net.

A HANDBOOK FOR MOTHERS: PRACTICAL ADVICE ON PREGNANCY AND MOTHERHOOD, by C. Phyllis Armitage, with a Foreword by Gerald Quin Lennane, M.C.; 1929. London: John Bale, Sons and Danielsson, Limited. Crown 8vo., pp. 134. Price: 2s. net.

THE PRINCIPLES OF APPLIED ZOOLOGY, by Robert A. Wardle, M.Sc.; 1929. London: Longmans, Green and Company. Demy 8vo., pp. 439, with illustrations. Price: 21s. net.

HOW TO STAIN THE NERVOUS SYSTEM: A LABORATORY HANDBOOK FOR STUDENTS AND TECHNICIANS, by J. Anderson, with an Introduction by J. G. Greenfield, B.Sc., M.D., F.R.C.P.; 1929. Edinburgh: E. and S. Livingstone. Crown 8vo., pp. 138. Price: 5s. net.

OUTLINES OF DENTAL SCIENCE, Volume X: Dental Histology, by Alexander Livingston, M.D.S., M.B., Ch.B. (Liv.), L.D.S., R.C.S. (England); 1929. Edinburgh: E. and S. Livingstone. Crown 8vo., pp. 143, with illustrations. Price: 7s. 6d. net.

Diary for the Month.

MAR. 26.—New South Wales Branch, B.M.A.: Council.
MAR. 27.—Victorian Branch, B.M.A.: Council.
MAR. 28.—South Australian Branch, B.M.A.: Branch.
APRIL 2.—Eye, Ear, Nose and Throat Section, South Australian Branch, B.M.A.
APRIL 3.—Victorian Branch, B.M.A.: Branch.
APRIL 3.—Western Australian Branch, B.M.A.: Council.
APRIL 4.—South Australian Branch, B.M.A.: Council.
APRIL 5.—Queensland Branch, B.M.A.: Branch.
APRIL 9.—Tasmanian Branch, B.M.A.: Branch.
APRIL 9.—New South Wales Branch, B.M.A.: Ethics Committee.
APRIL 10.—Federal Committee of the B.M.A. in Australia.
APRIL 10.—Central Northern Medical Association, New South Wales.
APRIL 11.—Victorian Branch, B.M.A.: Council.
APRIL 11.—New South Wales Branch, B.M.A.: Clinical Meeting.

Medical Appointments.

Dr. A. J. P. Chapman (B.M.A.) has been appointed Honorary Assistant Dermatologist at the Royal Alexandra Hospital for Children, Sydney.

* * *

Dr. J. P. Findlay (B.M.A.) has been appointed Temporary Honorary Relieving Ear, Nose and Throat Surgeon to the Royal Alexandra Hospital for Children, Sydney.

* * *

Dr. Robert Maxwell McMaster (B.M.A.) has been appointed Deputy Medical Superintendent of the Coast Hospital, Sydney.

Medical Appointments Vacant, etc.

For announcements of medical appointments vacant, assistants, *locum tenentes* sought, etc., see "Advertiser," page xvi..

ALFRED HOSPITAL, VICTORIA: Medical Appointments.
CHARTERS TOWERS DISTRICT HOSPITAL: Resident Medical Officer.
DAYLESFORD DISTRICT HOSPITAL: Resident Medical Officer.
LAUNCESTON PUBLIC HOSPITAL: Junior Resident Medical Officer.
NEW SOUTH WALES BRANCH OF THE BRITISH MEDICAL ASSOCIATION: Medical Secretary.
PERTH HOSPITAL, WESTERN AUSTRALIA: Pathologist.
RENWICK HOSPITAL FOR INFANTS, SUMMER HILL, NEW SOUTH WALES: Honorary Physician.
ROYAL PRINCE ALFRED HOSPITAL: Honorary Vacancies.
THE ADELAIDE CHILDREN'S HOSPITAL, INCORPORATED: Honorary Assistant Surgeon, Honorary Anæsthetist.
THE BRISBANE AND SOUTH COAST HOSPITALS BOARD: Resident Medical Officer.
THE CHILDREN'S HOSPITAL, INCORPORATED, PERTH, WESTERN AUSTRALIA: Junior Resident Medical Officers.

Medical Appointments: Important Notice.

MEDICAL practitioners are requested not to apply for any appointment referred to in the following table, without having first communicated with the Honorary Secretary of the Branch named in the first column, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

BRANCH.	APPOINTMENTS.
NEW SOUTH WALES: Honorary Secretary, 30 - 34, Elizabeth Street, Sydney.	Australian Natives' Association. Ashfield and District United Friendly Societies' Dispensary. Balmain United Friendly Societies' Dispensary. Friendly Society Lodges at Casino. Leichhardt and Petersham United Friendly Societies' Dispensary. Manchester Unity Medical and Dispensing Institute, Oxford Street, Sydney. North Sydney Friendly Societies' Dispensary Limited. People's Prudential Assurance Company, Limited. Phœnix Mutual Provident Society.
VICTORIAN: Honorary Secretary, Medical Society Hall, East Melbourne.	All Institutes or Medical Dispensaries. Australian Prudential Association Proprietary, Limited. Mutual National Provident Club. National Provident Association. Hospital or other appointments outside Victoria.
QUEENSLAND: Honorary Secretary, B.M.A. Building, Adelaide Street, Brisbane.	Members accepting appointments as medical officers of country hospitals in Queensland are advised to submit a copy of their agreement to the Council before signing. Brisbane United Friendly Society Institute. Stannary Hills Hospital. Boonah District Hospital.
SOUTH AUSTRALIAN: Secretary, 207, North Terrace, Adelaide.	All Contract Practice Appointments in South Australia. Booleroo Centre Medical Club.
WESTERN AUSTRALIAN: Honorary Secretary, 65, Saint George's Terrace, Perth.	All Contract Practice Appointments in Western Australia.
NEW ZEALAND (WELLINGTON DIVISION): Honorary Secretary, Wellington.	Friendly Society Lodges, Wellington, New Zealand.

Medical practitioners are requested not to apply for appointments to position at the Hobart General Hospital, Tasmania, without first having communicated with the Editor of THE MEDICAL JOURNAL OF AUSTRALIA, The Printing House, Seamer Street, Glebe, New South Wales.

Editorial Notices.

MANUSCRIPTS forwarded to the office of this journal cannot under any circumstances be returned. Original articles forwarded for publication are understood to be offered to THE MEDICAL JOURNAL OF AUSTRALIA alone, unless the contrary be stated.

All communications should be addressed to "The Editor," THE MEDICAL JOURNAL OF AUSTRALIA, The Printing House, Seamer Street, Glebe, Sydney. (Telephones: MW 2651-2.)

SUBSCRIPTION RATES.—Medical students and others not receiving THE MEDICAL JOURNAL OF AUSTRALIA in virtue of membership of the Branches of the British Medical Association in the Commonwealth can become subscribers to the journal by applying to the Manager or through the usual agents and booksellers. Subscriptions can commence at the beginning of any quarter and are renewable on December 31. The rates are £2 for Australia and £2 5s. abroad *per annum* payable in advance.